Heredity

AN INTRODUCTION TO GENETICS

THIRD EDITION

A. M. WINCHESTER

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About the Author

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Dr. Winchester is widely known for his writings in the fields of genetics and biology. He is the author of seven other books and four laboratory manuals, several of which have been translated into foreign languages. In addition he has contributed to numerous journals in his fields and has written many popularized articles for newspapers and magazines. He has served as president of the Florida Academy of Science and the Academy Conference of the American Association for the Advancement of Science. He is a fellow of the association and a member of the Genetics Society of America, the Society of Human Genetics, and Sigma Xi.

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Preface

This book presents the principles of heredity, or genetics, in a concise, easily understood form. As a volume in the Barnes & Noble Outline Series, it will provide students of genetics with a supplement to their classroom notes and textbook that will facilitate study and review. It should also be of value to those in other fields who need information on the fundamentals of heredity and to the general reader who wants to know more about this fascinating subject.

Because our knowledge of genetics has expanded at such an explosive rate during the past few years, there is need for a book that surveys the various fields which have emerged and gives an overview of the entire subject. Human genetics is emphasized because it has wide appeal and many valuable applications. Many of the basic principles of heredity can now be illustrated by human examples.

At the end of each chapter are problems related to the principles covered. These problems involve an understanding and application of these principles and not a mere recall of facts. Answers are given at the back of the book. It is suggested that these be referred to only after an attempt has been made to answer the questions. The book is liberally illustrated with photographs and drawings. Those photographs not credited to others are the work of the author.

Contents

1. METHODS AND APPLICATIONS OF GENETICS

Genetics, the study of heredity, is a relatively new science. Almost all of our knowledge in this field has been obtained in the present century and most of it since 1950. Each year many new applications are discovered, many of which have proved to have great practical value. This chapter will explain the methods used in genetic investigations and give examples of how genetic knowledge is being used; it will also describe the main branches of the science.

METHODS OF GENETIC STUDY

Our extensive knowledge of heredity has been acquired by a number of different methods of investigation. These include experimental breeding, statistical analysis, cytology, and biochemical genetics studies.

Experimental Breeding. If you wanted to determine how a certain trait in dogs was inherited, you would breed dogs exhibiting the trait to those that did not and analyze their offspring for several generations of controlled breeding. Many of the principles of genetics have been discovered by experimental breeding of this kind.

When selecting organisms for genetic investigations, several criteria must be met in order to obtain reliable results in a reasonable time.

1. A short life cycle. Elephants would be a poor choice for experimental breeding because they take years to reach sexual maturity and have such long gestation periods. Hundreds of years would be required to obtain sufficient numbers of offspring for proper statistical analysis. Mice, on the other hand, are ready for breeding about six weeks after birth and have a short gestation

period. Thus they are a frequent choice for experimental breeding.

2. A large number of offspring. Breeding experiments have little value without large numbers of offspring because it is the ratio of one kind of offspring to another that indicates how traits are inherited, and ratios are unreliable when numbers are small. As a result those organisms are favored that yield large numbers of offspring from each cross.

3. Variation in inherited characteristics. It would not be possible to learn how the position of ears is inherited in dogs if all had the same kind of ears. There are some dogs, however, with erect ears and others with drooping ears, so we can cross these two variant forms and learn how ear position is inherited. Geneticists therefore use organisms for breeding that exhibit a number of variations in their inherited characteristics.

4. Convenience and economy. The care and feeding of experimental animals can be very costly. Because large mammals usually require much time and money before sufficient numbers of offspring can be obtained, smaller mammals are studied more extensively. Mice are favorites because their care can be mechanized. At the great genetic laboratories in Oak Ridge, Tennessee, an entire building is given over to raising mice. They are fed and watered by conveyor belts, and the cages are cleaned simply by winding up long rolls of paper that line the bottoms.

A number of insects, however, are even more satisfactory in this regard. The little fruit fly, *Drosophila,* was one of the first used and is still very popular for genetic investigations. A single pair of these small flies can yield over a hundred offspring within ten to fifteen days in a vial containing only a few cents' worth of food. In addition these flies show hundreds of genetic variations, which can be clearly seen when they are etherized and examined under a microscope. Since it has been established that the method of inheritance is basically the same in all forms of life, the information gained through investigations of fruit flies can be applied to other forms of life including man.

Plants, on the whole, are more conveniently raised than animals. Once seeds are planted, plants require relatively little attention until they are mature. Many, however, have only one generation cycle per year, a disadvantage for experimental breeding. Corn and barley have been favorites of geneticists investigating the higher plants.

Microorganisms have been widely used for genetic research in

Fig. 1-1. The little fruit fly, Drosophila melanogaster, *is used extensively for genetic breeding experiments. The male is on the left and the female is on the right.*

recent years. A few bacteria placed in a culture tube can grow into millions within 24 hours, and the cost of the medium upon which they grow is very small. Bacteria might seem to be poor subjects for genetic investigations because of a paucity of variable morphological traits, but they differ greatly in their physiological reactions. Some are more resistant to antibiotics than others, some can utilize certain food elements while others cannot, and some produce certain products that others do not. Yeasts, molds, and certain algae are other microorganisms that are studied extensively.

Statistical Analysis. Results obtained through experimental breeding must be analyzed statistically in order to draw any significant conclusions. Probabilities and ratios are an important part of the study of heredity since the union of reproductive cells is a chance occurrence. In some forms of life experimental breeding is not possible; in these cases statistical methods must be applied to observations of crosses that have already occurred. Human inheritance is an example. We cannot breed human beings, but we can study the characteristics of children of couples who show the traits we are interested in. By statistical analysis of many families we can get reliable results. Family pedigrees are often constructed to give a visual representation of the pattern of trait transmission. In such pedigrees males are represented by squares and females by circles. Marriage is indicated by horizontal lines connecting the marriage partners, and children are shown attached to vertical

EARLOBE PEDIGREE

iden.
twins

frat.
twins
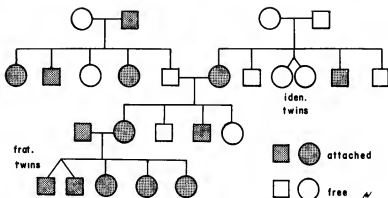
▨ ⊘ attached

☐ ◯ free

Fig. 1–2. Pedigree charts are used to visualize the inheritance of human traits. A study of this one indicates that attached earlobes, top left, is a recessive trait, while free-hanging earlobes, top right, is the alternate dominant.

lines. All those who show the trait under investigation are indicated by shading the squares and circles. An analysis of the pedigree shown in Figure 1–2 indicates that the characteristic of attached earlobes, as opposed to free-hanging earlobes, probably results from a recessive gene.* For definite conclusions more pedi-

* A recessive gene is one that does not manifest itself when a dominant gene controlling the same trait is present.

grees would have to be considered. Many breeders of large animals such as cattle and horses keep complete pedigrees so they can trace the transmission of traits.

Cytology. Cytology is the detailed study of cells. Since genes, the units of heredity, lie within cells, it is here that the reactions related to heredity must be initiated. A microscopic study of cells at certain times reveals rodlike bodies known as chromosomes, which are the carriers of the genes. The activities of the chromosomes during the process of cell division are therefore reflections of the activities of the genes. Geneticists who specialize in this area of study are known as cytogeneticists.

Biochemical Genetics Studies. As the techniques of biochemistry have developed, geneticists have used them to try to gain an understanding of the methods of gene action. For example, it was learned early in the study of human genetics that albinism in man was inherited as a recessive trait. When both parents carry the recessive gene the trait will appear in about one-fourth of their children. Such children lack the pigment melanin, which gives the brown color to skin, hair, and eyes. Geneticists wondered why this gene acts to prevent melanin formation. Biochemical investigations gave the answer. The cells of albinos cannot produce a certain

Fig. 1–3. Albino sister and brother. Biochemical genetics has shown that they carry genes which cannot produce an enzyme needed for the formation of melanin in the hair, skin, and iris of the eyes.

enzyme that converts the amino acid tyrosine into melanin. Through other biochemical studies it was found that many genes have their effect through enzymes, which they produce within the cells. Biochemical genetics is commonly studied in microorganisms because their chemical environment is relatively easy to control and analyze. Such research with lower forms has provided an understanding of human genetic abnormalities and methods of preventing them.

Biochemical tests of human blood and other tissues have been devised that can reveal the carriers of certain harmful traits caused by recessive genes. A person can carry one such gene without suffering any harmful effects if he also has a dominant alternate gene for a normal condition. Chemical tests, however, often reveal slight differences between the carriers and noncarriers. Many couples about to get married or start their families would like to know if they are carriers and if a very harmful trait has a high probability of appearing in their offspring. If they find that the chance is high, they may decide to forgo parenthood or turn to adoption. It is even possible to make tests of amniotic fluid and cells removed from around a fetus as early as twelve weeks after conception. Over forty different abnormalities can be detected by these techniques. Liberalized abortion laws permit a therapeutic abortion when it is found that the child will be greatly abnormal and when the parents' moral convictions make such a decision possible. Then they may wish to start another pregnancy with hopes for better luck.

BRANCHES OF GENETICS

Genetics has expanded so rapidly that no one person can become expert in all its aspects. It is now subdivided into a number of branches of specialization.

Microbial Genetics. Microbes include bacteria, yeasts, viruses, and certain molds, algae, and protozoa. We have already noted that many important genetic findings have been made through the study of these microscopic organisms. Even viruses, which can be seen only with extremely high magnification of the electron microscope, have been investigated extensively. They have quite a number of genes and show many variable genetic characteristics.

Molecular Genetics. When physicists and chemists collaborated

with geneticists in the investigation of heredity, molecular genetics was born. Chemical analysis revealed the nature of the material of which genes are made. It was found to be deoxyribonucleic acid (DNA), which is closely linked to certain proteins within the chromosomes. Then it was learned how genes exert their influence by sending chemical messages out into the cytoplasm of the cell. Now investigations are giving us clues to the forces that stimulate genes to operate at certain times and to cease their function at others. The answers to these questions can help us in our fight to control cancer and may even show us a way to restore damaged body organs, such as hearts and kidneys.

Cytogenetics. Cytogeneticists study the structure of chromosomes and how they are duplicated and segregated during cell division. Many improvements in cultivated plants have resulted from applications of cytogenetic discoveries. Improved varieties of rice, wheat, and corn are examples. A new era in human cytogenetics dawned with the discovery of ways to see chromosomes clearly in tissue culture cells from blood. Many human abnormalities proved to be the result of irregular distributions of chromosomes. Today many hospitals make routine examinations of the chromosomes of newborn infants to detect abnormalities of sex or other body defects early enough to begin effective treatment. Prenatal detection of abnormalities is even possible by studying chromosomes in the cells of amniotic fluid removed early in embryonic life, as described earlier in this chapter.

Human Genetics. Early attempts to study human heredity were discouraging because the pattern of transmission of many human traits did not seem to follow that of peas and fruit flies. Some geneticists even suggested that humans might have a unique method of inheritance. As techniques for study became more refined, however, it was evident that human heredity followed the same patterns of other forms of life. This led to a great upsurge in interest in human genetics. A number of human afflictions have been found to have a genetic basis, and through genetic understanding many of these have been overcome and prevented.

Human geneticists are frequently called upon to testify in legal disputes. Disputed parentage can often be resolved by a study of the inherited blood characteristics of the parties involved. Child legitimacy, estate inheritance, divorce, and possible hospital mixups of babies are some cases where geneticists can be of value.

APPLICATIONS OF GENETICS

Many of the discoveries that have been made in genetic research have proved to have important practical applications, especially in the fields of horticulture and animal husbandry.

Genetics Applied to Horticulture. The principles of genetics were being applied to horticulture long before we had any knowledge of the methods of heredity. Selection was the primary method used. Only those seeds were planted that came from plants which had the most desired traits, and after many generations of selection superior varieties were established. As an understanding of the principles of genetics developed during this century, however, crop yield has taken a giant leap forward. We now obtain more than twice as much corn per acre as we did at the turn of the century. Without this great increase in yield we could not feed ourselves, much less export food to other countries. Now there is a worldwide food shortage, and plant geneticists are working to produce high-yielding varieties adapted to soil and climatic conditions of countries that are unable to meet the food needs of their populations.

There has also been a great improvement in the quality of agricultural products. You could not enjoy a Delicious apple or a sweet,
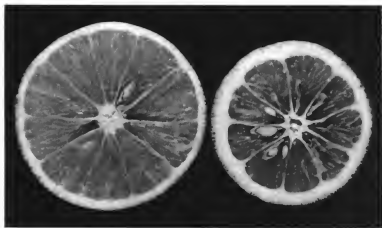
Fig. 1–4. Application of genetic principles has resulted in great improvement of many cultivated plants. The sweet, juicy, thin-skinned orange at left has been produced from the sour, heavily seeded, wild orange shown at right.

juicy Valencia orange had it not been for the efforts of plant geneticists. The many beautiful flowers we enjoy also represent the culmination of extensive applications of genetic knowledge.

Genetics Applied to Animal Husbandry. Much that has been said about genetics in horticulture applies to animal husbandry. The fat cattle that give us our choice and prime steaks are far removed from the scrawny animals that once grazed our western plains. Hogs today are leaner than in the past when they were bred to give a high lard yield; in fact, all modern breeds are quite different from the wild hogs from which they were derived. Sheep have a much higher wool yield as a result of breeding and selection. Breeds of chickens have been developed that grow fast and are ready for market earlier than they used to be, while other breeds produce hens that lay large numbers of eggs. Turkeys now being bred with very broad breasts to give much tender white meat present a contrast to the wild turkeys with smaller breasts of dark meat that the Pilgrims found here when they landed.

Fig. 1–5. Domestic animals have been greatly improved by geneticists. The bull on the right is a much better beef producer than the lean, long-horned steer at left. Likewise, the wild boar on the left is much less valuable as a pork producer than the black Hampshire boar at right. (U.S. Dept. of Agriculture photos.)

PROBLEMS

At the end of each chapter, problems are given that may be used as a self-test to check your understanding of the chapter. It is suggested that you answer these problems to the best of your ability without referring back to the chapter. Then make corrections by checking the material in the chapter. Finally, you can refer to the appendix at the back of the book where the answers to these problems are given.

1. Cattle are important domestic animals, and you would like to know more about their heredity. Evaluate cattle according to each of the criteria for an ideal animal for experimental breeding.

2. In light of your answer to question 1, why do many cattlemen keep careful pedigrees of their stock?

3. Physicians in the past concentrated most of their energies on the prevention and cure of diseases caused by germs. Today more and more of their efforts are going into prevention and treatment of diseases caused by genes. Why do you think this change has come about?

4. In recent times new varieties of rice have been developed in the United States that give a much higher yield than the varieties used in many areas of Asia, where the people suffer from chronic malnutrition. Great hopes were held for these new varieties, but the results have been disappointing. Why do you think this has been the case?

2. BACKGROUND OF MODERN GENETICS

People have long been curious as to why children look like their parents, domestic animals reflect the characteristics of their progenitors, and seeds grow into plants like those that produced them. Although ancient peoples had some fanciful speculations about heredity, they put into practice some of the principles even though they did not understand them. A Babylonian tablet dating back to about 4000 B.C. gives the pedigree of five generations of horses showing how characteristics of the head and mane were transmitted. Stone carvings from ancient Egypt show men cross-pollinating the date palm, with the obvious purpose of improving the quality of the fruit. The ancient Chinese developed improved varieties of rice. The many breeds of dogs that exist today show
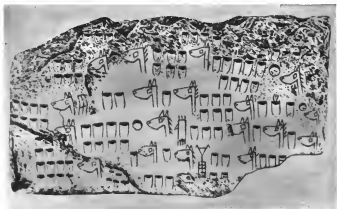
Fig. 2–1. An ancient horse pedigree. This stone tablet over five thousand years old was excavated in the Middle East. It shows inheritance through five generations. Three types of mane are shown (erect, pendant, and maneless) and three types of profile (convex, straight, and concave). (From Amschler, Journal of Heredity.)

that our ancient ancestors used hybridization and selection to produce the type of dog best suited to their particular needs. Some of the old Hebrew laws indicate that the Hebrew people understood the principles of inheritance of certain human traits. One of these laws exempted boys from circumcision if they were born of women who came from families with a history of boys who bled excessively. Sons of men from such families were not exempt. This shows a recognition of the principle of sex-lined inheritance as applied to hemophilia.

ANCIENT GREEK SPECULATIONS

Some of the earliest recorded attempts to explain heredity were made by Greek philosophers who lived before Christ.

Pythagoras. Pythagoras, who died about 500 B.C., proposed that a moist vapor descends from all parts of a man's body during sexual intercourse. As it reaches the reproductive organs, it condenses and forms the semen, which, in turn coagulates to form an embryo within the body of the woman. This embryo will resemble the male parent because the semen will develop body parts like those from which it came. This concept held sway for many centuries. A picture of a man and a woman in intercourse drawn in 1493 by Leonardo da Vinci showed, in transparency, a number of tubes leading from all over the man's body to his reproductive organs. Medical books as late as the seventeenth century showed pictures of the stages of coagulation of semen to form an embryo.

Empedocles. The problem with Pythagoras' hypothesis was that it made no provision for the inheritance of characteristics from the mother, although it was assumed that developing in her body would have some effect. Another philosopher of the same period, Empedocles, proposed that the woman also produced a semen, one that blends and coagulates with the male semen to produce the embryo. He reasoned that not all of the semen from either parent was used; thus a child could show some traits of one parent and some of the other.

Aristotle. Aristotle, who lived some 200 years later, proposed that blood was the element of heredity, passing continuously from parents to children down through the generations. The semen of the male was taken to be highly purified blood, while that of the

female, which he supposed to be the menstrual fluid, was less highly purified. This female "semen" was supposed to furnish the building material for the embryo, while the male semen gave it form and life. Since Aristotle was held in such great esteem, this concept of heredity dominated genetic thought for some 2000 years and even today we find remnants of belief in it. We use the terms *blood relative, blue blood, royal blood, bad blood,* and *blood line,* all indicating an effect of blood on heredity.

DISCOVERY OF THE PHYSICAL BASIS OF HEREDITY

During the seventeenth and eighteenth centuries a number of discoveries were made and theories proposed that led to an understanding of the physical basis of heredity.

William Harvey and His Study of Embryos. During the early part of the seventeenth century William Harvey (1578–1657), well known for his discovery of the circulation of the blood, decided to test Aristotle's theory. He mated twelve female deer and killed six of them at various stages of pregnancy. He found nothing like coagulating semens in the early stages, but he did see a little rounded body attached to the uterus of a deer that had been mated several weeks before. Examination of deer in progressively later stages of pregnancy showed that this body was gradually transformed into a baby deer. In incubating chicken eggs he noticed a small streak on the yolk that gradually changed into a chick. On the basis of these observations he suggested that mammals produce eggs like birds, only they are much smaller, and that these grow into embryos when the uterus is "magnetized" by the friction of intercourse. He considered the role of the semen to be a vitalizing one.

Anton van Leeuwenhoek and the Discovery of Sperm. The invention of the microscope in the latter part of the seventeenth century opened the way for the discovery of sperm. Of the several observers who reported small wiggling organisms within human semen, the best known is Anton van Leeuwenhoek (1632–1723), a Dutchman who ground his own lenses and made a microscope capable of considerable magnification. He also found sperm in the semen of other animals. On noting the association of frog sperm with frog eggs, he suggested that the union of these two resulted

in the formation of an embryo. The people of the time were slow to give up their old concepts, however, and many argued that the sperm were really just parasites in the semen and had nothing to do with embryo formation. The consistent presence of sperm in all semen, however, indicated that they must be involved with reproduction in some way.

The Preformation Theory. Another Dutch scientist, **Jan Swammerdam** (1637–1680), speculated that each sperm contained a miniature human being which required only the protection and nourishment provided by the uterus to grow into a baby. This preformation theory attracted many adherents. Some drawings of the time show the supposed presence of tiny babies within the heads of sperm (figure 2–2).

Discovery of Mammal Eggs. Still another Dutch scientist, **Regnier de Graaf** (1641–1673), compared the ovary of mammals with that of birds and found many similarities. Both devel-
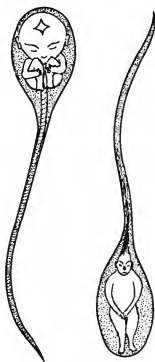
Fig. 2–2. Some early investigators imagined that they could see small embryos within the head of human sperm. These drawings represent their interpretations. (Left, after Hartsoeker, 1694, right, after Dalempatius, 1699.)
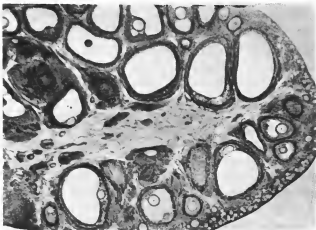
Fig. 2–3. *Human eggs within Graafian follicles in the ovary. It was the similarity of these to the larger follicles of birds which led to the conclusion that mammals produce eggs as well as birds.*

oped swollen bodies, now known as Graafian follicles, that burst and released eggs, although the mammalian egg is much smaller than the bird egg. He found cases of human extrauterine gestation, which supported his idea that some human eggs fail to make it into the uterus for development.

The Incapsulation Theory. As the concept of mammal eggs came to be accepted, **Charles Bonnet** (1720–1793), a Swiss scientist, proposed the incapsulation theory, which held that the potential embryos were in the eggs, not in the sperm. He went on to suggest that each female animal contains within her body the "germs" of all the offspring that will ever descend from her, one generation within the other, somewhat like a series of Chinese boxes. In each generation the outer box expands and differentiates to form an embryo. According to this theory, when the innermost box is used there will be no more descendants. Bonnet's study of aphids, which can have a succession of generations of females without fertilization, led to the formation of this theory.

Epigenesis. Kaspar Friedrich Wolff (1733–1794) supported the concept of epigenesis as opposed to preformation. This theory held that reproductive cells do not contain embryos but small particles that have the power to organize the body parts. Wolff based his theory on extensive studies of the developing chick embryo.

The Frenchman **Pierre Louis Moureau de Maupertuis** (1698–1759) had already proposed the existence of such particles and even suggested that such a particle from one parent could be dominant while that from the other parent could be recessive. All of this is quite similar to our present knowledge about genes within the reproductive cells.

Discovery of Nucleic Acid. In 1869 a Swiss physician, **Friedrich Miescher**, began a chemical analysis of the pus cells that adhered to the bandages he removed from infected wounds. He treated these cells with dilute hydrochloric acid, which dissolved most of the cytoplasm but left the nuclei intact. He then treated the nuclei with pepsin, which digested the protein, leaving a gelatinous material he called nuclein. Studies on the sperm of Rhine salmon showed that the sperm head is 49% nuclein. Miescher concluded from this evidence and studies on many other types of cells that nuclein is present in all cells and must be related to heredity. The role of nucleic acid, as nuclein came to be called, was finally proven in the mid-twentieth century. As its exact chemical nature became known, it was called deoxyribonucleic acid (DNA). It is now recognized as the material of which genes are made.

Discovery of Chromosomes. In 1875 two German biologists, **Walther Flemming** and **Eduard Strasburger**, noted rodlike bodies within the cells of both plants and animals that were in the stages of division. Since these stained heavily with certain basic stains that were brightly colored, they became known as **chromosomes**. In 1882 **Edouard van Beneden**, while observing the union of the sperm with the egg of the roundworm, *Ascaris*, noted two chromosomes from each parent uniting to give the four chromosomes found in other body tissues. This showed that the chromosome number is reduced to one-half when reproductive cells are formed and is restored to its full number at fertilization.

THE CONCEPT OF INHERITANCE
OF ACQUIRED CHARACTERISTICS

Widely believed during the nineteenth century was the idea that the characteristics acquired by organisms during their lifetimes as adaptations to the environment can be passed on to their offspring.
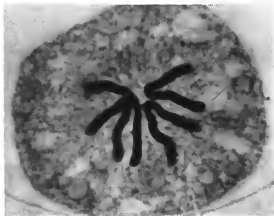
Fig. 2–4. Chromosomes, the carriers of the genes of heredity. These are typical chromosomes as seen when a cell is in process of preparation for division. This cell is from a parasitic worm, known as Ascaris, which has only four chromosomes in each of its body cells.

Use and Disuse. A Frenchman, **Jean Baptiste Lamarck** (1744–1829), emphasized the easily confirmed fact that animals tend to develop those body parts which are used extensively, while those not used tend to deteriorate. A man who does heavy manual labor certainly will have larger and stronger muscles than a man who has a sedentary occupation. When an arm or a leg cannot be used because it is paralyzed, the muscles gradually deteriorate. A fair-skinned person exposed to the sunlight develops a protective layer of melanin within the cells of his skin. This adaptability became known as the principle of use and disuse. Lamarck contended that these adaptations of individuals were somehow transferred to future generations through heredity, a principle that became known as the **inheritance of acquired characteristics.** He theorized that wading birds have long necks because each successive generation of these birds stretches the neck more and more as they reach down into the water for food. As an example of disuse he cited the toothless ant bear, holding that since the ancestors of these animals swallowed their food without using their teeth, the teeth gradually dwindled in size until they were gone. He even said that we could produce a race of one-eyed human beings if we removed the left eye of a group of children at birth for many generations.

Pangenesis. The famous English naturalist **Charles Darwin** (1809–1882) is best known for his theory of natural selection as a method of evolution. This theory was based on four premises. First, there is an overproduction of offspring. Second, there are hereditary variations among these offspring. Third, there is a struggle for existence. Fourth, there is a survival of the fittest: Those with the most favorable characteristics survive and pass these favorable traits to their offspring.

One part of the theory bothered Darwin. What was the source of the hereditary variations that were necessary if there were to be any selection? He eventually proposed the provisional hypothesis of pangenesis, which held that tiny pangenes, or gemmules, were produced in all parts of the body and migrated to the reproductive organs where they formed like parts in the embryo. This would allow for the inheritance of acquired characteristics. We now recognize the validity of Darwin's theory of natural selection, but this hypothesis of pangenesis, so reminiscent of Aristotle's old idea, has been proved to be false.

The Germ Plasm Theory. During the latter part of the nineteenth century the German biologist **August Weismann** (1834–1914) decided to test the concept of inheritance of acquired characteristics. His most famous experiment was the one in which he cut the tails off newborn mice for 22 generations. When the tails of mice in the next generation were allowed to grow, however, they were just as long as in mice that had no lineage of mutilated ancestors. Noting the potential immortality of the protoplasm in one-celled animals as they reproduce by repeated fissions, he formulated the idea of the continuity of the germ plasm of higher animals. In essence, he proposed that **germ plasm** is isolated early in embryonic life from the rest of the body, which he called **somatoplasm.** From then on the germ plasm lives as a parasite on the somatoplasm, contributing nothing to the welfare of the individual and not being influenced by anything done by the individual. Thus the germ plasm flows in a continuous stream, blending with the germ plasm of a sexual partner at each new generation.

The Mutation Theory. Weismann's theory, however, made no provision for any changes in heredity, changes that must occur if there is to be evolutionary development. Selection alone cannot account for such changes because selection would run out of new
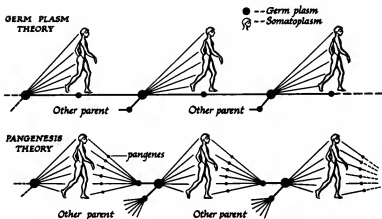
Fig. 2-5. The germ plasm theory of Weismann contrasted with the pangenesis theory of Darwin. Weismann pictured the germ plasm as a continuous stream producing somatoplasm as it flowed through the generations. Darwin thought of each generation as producing the germ plasm of the next generation. (From Winchester, Genetics, 4th ed., Houghton Mifflin.)

material to select from without an input of new characteristics. This problem was solved by a Dutchman, **Hugo De Vries** (1848–1935). He noted unusual forms of evening primroses growing among the more common types in the meadows of Holland. Among these rare forms were plants with dwarfed bodies, double petals, and unusual leaf types. He transplanted some of these into his garden and found that they produced offspring like themselves. These observations led to the mutation theory, which held that the elements of heredity can undergo sudden changes unrelated to the external environment, changes that are passed down through future generations in their altered state. Today we know that mutations occur in all forms of life, although we have since learned that the so-called mutations observed by De Vries were actually due to chromosome aberrations and not to changes in individual genes.

The Lysenko Controversy. Although the theory of the inheritance of acquired characteristics has been disproved by many genetic studies, there is still some lingering belief in the possibility of the transmission of such characteristics. Even in scientific meetings a geneticist may present what he considers is evidence to support a revival of the refuted theory. Any such supposed evidences

are easily discredited, but there was one case in which official governmental approval was given with tragic consequences for the country involved.

In the Soviet Union an obscure plant breeder, **Trofim D. Lysenko**, did some experiments on wheat and tomatoes during the 1930s. He found that by increasing the amount of fertilizer he could obtain larger and more productive plants and thought that the descendants of these plants also were larger and more productive. He then proposed measures that would greatly increase the yield of Russian agriculture based on the inheritance of acquired characteristics. His plan even included the improvement of domestic animals. Cows with high butterfat in their milk were to be produced by feeding calves rich cream for several generations. New breeds of chickens with high egg yield were to be produced by feeding protein-rich diets to the chicks for several generations. Lysenko was a clever politician and persuaded Joseph Stalin of the validity of his methods. The Central Committee of the Communist party soon issued a decree that this was to be the official policy of all geneticists in the Soviet Union. As time passed, however, it became apparent that Lysenko's plan was not working as he had claimed. The yield of wheat declined at a time when it was rising in other countries. When Stalin died and Khrushchev took over, there was some withdrawal of the strict support of Lysenko, and when Khrushchev lost his position, the Soviet leaders reinstated classical genetics. Today they have very good genetics programs going.

DISCOVERY OF METHOD OF TRANSMISSION OF INHERITED TRAITS

Gregor Mendel (1822–1884) is called the father of modern genetics because of his discoveries of the way in which inherited traits are passed from parents to their offspring. As a youth he joined the Augustinian monks in a monastery at Brno (now in Czechoslovakia) and was sent to the university at Vienna where he became interested in experiments on plant hybridization. When he returned to Brno he continued his experiments, using a small plot of ground beside the monastery for this purpose. He chose garden peas for his work because (1) they could be obtained in a number

of pure-breeding varieties, (2) they were usually self-pollinating, and (3) hybrids between different varieties were fully fertile. After eight years of performing various kinds of crosses among 22 varieties, he devised a model to explain inheritance of individual traits that has proved to be correct. (His experiments and conclusions are described in chapters 4 and 5.) But when he presented his findings before the Society of Natural Science in Brno in 1865, his colleagues failed to recognize their great significance. The rediscovery in 1900 of the report of his findings started modern genetics on its way.

Important discoveries during the present century have become too numerous to list in this tabulation, but many of these will be brought out in the chapters to follow.

PROBLEMS

1. Many people today still have some lingering impression that there can be inheritance of acquired characteristics. What definitive evidence could you present to them to try to make them see that there can be no such thing? (Consider some of the discoveries mentioned in this chapter as a basis for your recommendation.)

2. Lysenko proposed to revolutionize Soviet agriculture through application of what he presented as a new concept of heredity. How was his concept similar to those that had been proposed in previous centuries?

3. Giraffes have long necks that make it possible for them to feed on the leaves of tall trees. Tell how each of the following would have explained how the long neck developed: Lamarck, Darwin, De Vries.

3. THE PHYSICAL AND CHEMICAL BASIS OF HEREDITY

In the course of his work with garden peas, Gregor Mendel postulated the presence of "factors" as the physical units responsible for heredity. For many years these were hypothetical units that transmitted characteristics from parents to offspring. In recent times, however, we have been able to determine the exact chemical structure of these units, which we now call **genes.**

DNA, THE GENETIC MATERIAL

Chromosomes are made of **nucleoprotein,** compounds of proteins and nucleic acid. It was first assumed that the proteins were the genetic material because a protein molecule can show the almost infinite variety necessary to account for the many different kinds of genes that exist. There are twenty different kinds of amino acids, and a protein molecule may be made of hundreds of them. The nucleic acid, on the other hand, seemed to have a much simpler structure consisting of a sugar-phosphate and only four kinds of nitrogen bases. As the chemical structure of the nucleic acid was worked out, however, it was found to have a potential for great variety. It was identified as **deoxyribonucleic acid,** usually abbreviated **DNA.** Evidence accumulated that DNA was the material of which genes are made.

Evidence from Bacterial Transformation. The term *transformation* in genetics refers to the uptake of genes by an organism from its surroundings. Bacterial transformation was first demonstrated by Fredrick Griffith in 1928. The bacterium he worked with was *Diplococcus pneumoniae*, which causes one form of pneumonia. A virulent form of this organism consists of pairs of cocci surrounded by a polysaccharide capsule. When grown on a laboratory culture medium the colonies are smooth and shiny. There

also exists a nonvirulent strain that cannot produce the capsules and that forms rough colonies. Mice injected with the smooth strain sickened and died; those injected with the rough strain were not harmed. When bacteria of the smooth strain were killed by heat and then injected, however, the mice did not suffer any ill effects. A combination of heat-killed smooth and living rough bacteria was lethal. Smooth bacteria could be isolated from these dead mice. It was apparent that some of the living rough bacteria had picked up genes necessary to form capsules from the dead smooth bacteria. Since the protein portion of the smooth bacteria had been coagulated and rendered ineffective by heat, the DNA, which had not been destroyed by the heat, must have been the material that was taken up.

More conclusive evidence was provided by Avery, MacLeod, and McCarty in 1944. They found that when colonies of rough bacteria were grown on culture media to which DNA extracted from smooth colonies was added, some of the rough bacteria became transformed into smooth forms. Protein extracts from the
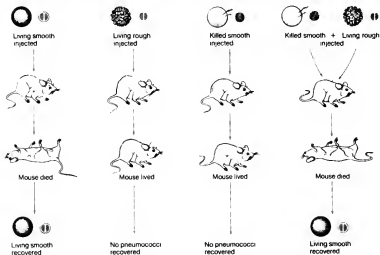

Fig. 3–1. Bacterial transformation. Within the living mouse some of the DNA from a virulent strain (smooth) is taken up by a nonvirulent (rough) strain which is then transformed into a virulent strain. The appearance of the colonies is shown at the left and the individual diplococci at the right. (Reprinted by permission of Houghton Mifflin from Winchester, Genetics, 4th ed.)

smooth colonies did not have their transforming power. The foreign DNA apparently adhered to the bacterial cell walls and was eventually incorporated into the chromosomes.

Some of the practical applications of the principle of bacterial transformation have proved discouraging. For example, it was found that chickens raised on feed to which the antibiotic aureomycin has been added grow faster because they are not subject to certain bacterial infections. If such feed is used extensively, however, selection tends to establish strains of bacteria with genes that make them resistant to the antibiotic. This is not all. Certain human pathogens, such as the *Salmonellas*, a common cause of food poisoning, that come in contact with these new strains, may pick up some of the genes for antibiotic resistance. When such transformed bacteria infect a human being, they cannot be readily destroyed by antibiotics of this nature.

Perhaps it will one day be possible to make certain defective human cells normal by means of the principle of bacterial transformation. Some people have genes that cannot produce a certain liver enzyme. If these cells could take up DNA from normal human cells or even from bacteria that produce the enzyme they might be transformed into cells that could produce the enzyme. Some preliminary success has been reported along these lines in experimental animals.

Evidence from Virus Investigations. Viruses consist of an outer protein coat and an inner core of nucleic acid. The nucleic acid of most viruses is DNA, but those that infect higher plants, such as the tobacco mosaic virus, may have the closely related **RNA (ribonucleic acid).** Working with the tobacco mosaic virus, H. Fraenkel-Conrat found that he could separate the outer protein coat and the inner core of RNA by osmotic shock, produced by placing the virus in alternate hypotonic and hypertonic solutions. The two parts would recombine, however, when placed in normal solutions, even if they came from different strains. The combination of the core from a highly virulent strain and the coat from one of low virulence resulted in a highly virulent virus; the reverse combination gave a virus of low virulence. This showed that the nucleic acid determined virulence.

More evidence that DNA is the genetic material came from studies on the virus that infects the bacterium *Escherichia coli.* Such a virus is known as a **bacteriophage,** or **phage.** This phage

has two main parts: a hexagonally shaped "head" containing the DNA and a tubelike "tail." In phage infection the tail becomes attached to the bacterial cell wall. The DNA within the head is then injected into the bacterium, where it undergoes duplication (replication). Soon, as many as fifty to one hundred prophage particles are present. These prophages acquire protein coats and become complete phages. Then the bacterial cell ruptures, releasing the many phage particles, each of which can infect another bacterium.

Hershey and Chase (1952) proved that it is the DNA, not the protein, that is transmitted from the phage into the bacterial cell. When radioactive sulfur (^{35}S) was incorporated into the phages and these were allowed to infect bacteria, radioactivity could not be detected inside the cells of the infected bacteria. Since sulfur is a part of some proteins but is not a part of DNA, this experiment showed that no protein entered the bacteria. When phages labeled with radioactive phosphorus (^{32}P) were permitted to infect the bacteria, most of the radioactivity was found within the bacterial cells. Phosphorus is a constituent of DNA, but not of protein; thus the DNA was transmitted into the bacterial cell and must be the material of heredity.

Evidence from Bacterial Transduction by Viruses. Zinder and Lederberg (1952) found that bacteriophages could carry genes of one bacterium to another bacterium. Their experiments were conducted with the mouse typhoid bacterium *Salmonella typhi-*
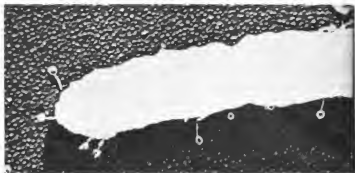

Fig. 3–2. Infection of the bacterium E. coli by a bacteriophage. The small virus particles become attached to the outside of the bacterium and inject their nucleic acid into the cell. (Electron photomicrograph by T. F. Anderson, E. Wollman, and F. Jacobs.)

murium. One strain of this organism could synthesize the amino acid threonine, but not methionine. It had the genes thr^+ and met^-. Another strain was just the reverse; it had thr^- and met^+. When a phage was grown on the first strain and then allowed to infect the second, some bacteria were recovered that could synthesize both amino acids; they were thr^+ and met^+. Apparently, the phage while forming in bacteria of the first strain picked up some of the genes of its host and transferred these to the second host bacteria. The gene met^+ must have been included. Such experiments are possible because some phages are temperate, that is, they do not destroy all the cells they infect, and the surviving cells can be tested for their enzyme production. Such an alteration of heredity through genes introduced by an invading virus is known as *transduction.*

Research is being conducted on the possibility that normal genes can be introduced by transduction into human cells with abnormal genes. There are many temperate phages that infect human cells with no serious damage to the body. The human immune reaction tends to reject transfer of entire cells from a normal donor, but if temperate viruses could be grown on tissue culture cells of a normal person and then be used to infect a person lacking a vital normal gene, perhaps some of the normal genes could be transduced into cells of the recipient.

Evidence from Quantitative DNA Measurements. DNA is found in all forms of life, with the exception of a few viruses that have the similar RNA. The amount of DNA in a cell can be measured by determining the amount of light transmitted through the nucleus of a cell stained by the **Feulgen reaction,** which stains DNA only. It can also be measured by the degree of ultraviolet ray absorption. DNA absorbs these rays when they have a wavelength of 2600 angstrom units. Finally, the DNA in a given amount of tissue can be extracted and weighed, and the quantity per cell calculated.

These studies show that a sperm cell has about half the DNA found in a somatic cell. This would be expected since sperm carry only half as many genes. Also the somatic cells from various parts of the body tend to have about the same amount of DNA, even though these cells vary greatly in size and structure. Table 3–1 shows the results of some of these measurements. There are some variations, but the figures all lie within the range of error expected

from the techniques used. The nucleus of an egg has about the same amount of DNA as a sperm and about half that of a somatic cell, as would be expected, but the DNA content of the entire egg may be higher. This is because DNA has also been found in certain organelles of the cytoplasm, as is discussed later in this chapter.

Measurement of the quantity of DNA also permits an estimation of the number of genes per cell. The average weight of a single gene, as calculated by the atomic weight of its individual parts, is about 10^{-18} gram. This figure can be divided into the total weight of DNA per cell to give the approximate gene number. Such calculations put the estimated number of genes in a human somatic cell as high as 300,000. In the domestic fowl the number drops to about 130,000, in fruit flies to 100,000, in *E. coli* (the common bacterium of the human colon) to 6000, and in the colon bacteriophage to 270. These variations are consistent with the complexity of these organisms. The protein portions of the cells do not show this consistent variation.

DNA STRUCTURE

In 1962 the Nobel Prize was awarded to James Watson and F. H. C. Crick for their discovery of the structure of DNA. They used x-ray diffraction photographs, chemical analysis, and physical data to construct a model that seemed to be the form of DNA: a double helix with two long strands held together by cross connections of paired bases. In shape it resembles a long, twisted ladder.

The outer strands are composed of five-carbon (pentose) sugar molecules, **deoxyribose sugar**, alternating with inorganic phosphate molecules. The paired bases making the cross connections are nitrogenous ring compounds of two kinds, **purines** with two rings and **pyrimidines** with single rings. Each cross connection is made of a purine paired with a pyrimidine. There are two kinds of purines, **adenine** and **guanine**, and two kinds of pyrimidines, **thymine** and **cytosine**. Furthermore, adenine is always paired with thymine and guanine is always paired with cytosine. This was suspected by Watson and Crick when they found that, although the quantity of the bases varied in cells from different organisms,

TABLE 3–1

AVERAGE QUANTITY OF DNA IN DIFFERENT CELLS

(expressed in 10^{-12} gram)

(data from Mirsky and Osawa, 1961)

	Sperm	Erythrocyte	Liver Cell	Kidney Cell
Man	3.25	no nucleus	10.36*	8.60
Domestic cattle	3.42	no nucleus	7.05	6.63
Domestic fowl	1.26	2.58	2.65	2.28
Fish (carp)	1.64	3.49	3.33	—

* Many of the human liver cells were found to contain the tetraploid rather than the diploid chromosome number, and this accounts for the relatively high weight of DNA per cell.

the adenine and thymine molecules were always about equal and the guanine and cytosine molecules were likewise equal. (See table 3–2.) Figure 3–3 shows how the various parts are put together. The unit comprising a base and its attached sugar-phosphate is known as a **nucleotide**.

The variety of genes is possible because of the extreme length of the DNA molecules. There are only four possible variations in the positions of the paired bases: adenine-thymine, thymine-adenine, guanine-cytosine, and cytosine-guanine. The entire DNA

TABLE 3–2

PERCENTAGE OF BASES IN DNA

(data from Chargaff, 1968)

	Adenine	Thymine	Cytosine	Guanine
Man	31.0	31.5	19.1	18.4
Cattle	28.5	27.2	22.1	22.0
Salmon	29.6	29.1	20.7	20.4
Sea urchin	32.7	32.1	17.6	17.4
TB bacterium	15.1	14.6	34.9	35.4

(The small variations in adenine-thymine and cytosine-guanine ratios are within normal fluctuations due to measuring error.)
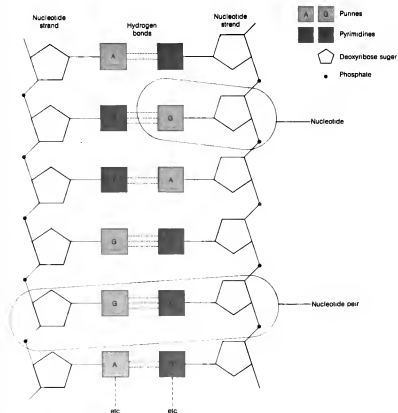
Fig. 3–3. Diagrammatic representation of a small portion of a DNA molecule showing the relationship of the various parts. (Reprinted by permission of Houghton Mifflin from Winchester, Genetics, 4th ed.)

molecule, however, may include hundreds of these paired nucleotides. A change of even one of them will make the gene different. Hence an almost infinite variety of genes is possible. This is explained more fully in chapter 16.

DNA REPLICATION

When a cell divides, the two cells produced normally have all the genetic potential of the original. This would not be possible

unless each gene within the cell first underwent an exact duplication called **replication.** The method of replication remained a mystery for many years, but the Watson-Crick model made possible a quite plausible explanation. When a cell reaches a certain point in its growth some stimulus makes the genes replicate in preparation for mitosis (nuclear division), which precedes cell division. Replication begins when the weak hydrogen bonds that hold the purine-pyrimidine bases together break apart. Each gene thus becomes two half genes with a single backbone strand and a single row of bases. The process of separation starts at one end and proceeds the length of the gene in a manner that can be compared to the unzipping of a zipper. As they separate, each half gene acts as a template for reconstructing the missing half. A nucleotide including thymine will attract to itself one containing adenine and so on for the other three bases. Thus as the DNA becomes "unzipped," the double helix is restored by combination with the missing compounds in the cell. These compounds are derived from the food eaten by the animal or produced by the plant. This explains why improper growth results from insufficient intake of vital food elements. Without the raw materials the genes cannot properly replicate.

DNA SYNTHESIS OUTSIDE THE CELL

In 1959 Arthur Kornberg and S. Ochoa received the Nobel Prize for their discovery of a way to bring about replication of DNA in vitro (in glass). To four kinds of nucleotide subunits they
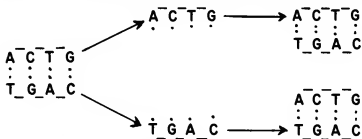
Fig. 3–4. Method of duplication of DNA. The two halves of the double helix become separated at their weak hydrogen bonds and each half attracts to itself the parts that have been lost.

added a polymerase enzyme from *E. coli* to initiate the synthesis, magnesium ions to activate the enzyme, and a little DNA primer. Later it was found that some DNA synthesis would take place without the primer if the mixture was allowed to stand for five or so hours. Such DNA, however, tended to have bases that alternated without the variation found in DNA from a living cell. For example, a single strand might consist of ATATATATAT—. Such a simple repetition of bases could never be expected to function as a gene. In 1967, however, Kornberg and Ochoa did synthesize biological active DNA and successfully introduced it into living bacteria.

GENE ISOLATION

In 1970 Jonathan Beckwith and co-workers at Harvard isolated a single gene from the bacterium *E. coli*. During bacterial transduction they were able to capture one of the genes before it became incorporated into the genetic system of the recipient. A photograph of the electron microscope image of the gene was made. This first picture of a gene shows the double helix structure and confirms the model constructed by Watson and Crick.

PROBLEMS

1. List the evidences that it is the nucleic acid core rather than the protein coat which determines the characteristics of a virus.

2. How does bacterial transformation differ from bacterial transduction?

3. A bacterium is infected by a phage, which then replicates to form prophages within the cell. The cell is broken open, however, before protein coats have been formed around the prophages. The liberated prophages are found to be noninfective. Explain why.

4. The quantity of DNA in somatic cells of different parts of the body of any species tends to remain constant, but there are great differences in the quantity in cells of different species. Explain.

5. A small part of a DNA molecule has the following sequence of bases on one side of the helix: adenine, thymine, cytosine,
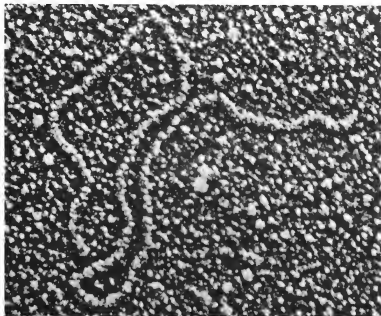
Fig. 3–5. Photograph of a single gene. This greatly magnified photograph shows a gene from E. coli. The double helix nature of the gene is apparent. (Courtesy Jonathan Beckwith.)

adenine, guanine, guanine. List the complementary bases that would be found on the other side of the helix.

6. When the four bases of DNA are extracted and separated from different tissues, the quantity of adenine and thymine is approximately equal, but the proportion of adenine to cytosine shows considerable variation in the tissues of different species. Explain.

4. MITOSIS AND MEIOSIS

Cells vary greatly in size and shape. Those in different tissues of the same organism show great diversity, and those in different species may show even greater diversity. All cells, however, have genes arranged on chromosomes, and all have some process whereby these genes and chromosomes duplicate and segregate so that daughter cells formed by cell division have the same kind of genes and chromosomes present in the parent cell. Some simple, mostly one-celled organisms, do not have a definite nucleus. They are known as **prokaryotes** and include bacteria, blue-green algae, and a few lesser-known forms. They have a single, circular chromosome that replicates, and then the cell undergoes fission and each daughter cell receives one chromosome. Most types of cells are **eukaryotes** and have a nucleus containing more than one chromosome. These cells undergo mitosis, a process that separates the replicated chromosomes before the cell divides. Meiosis is a variation of this process, which reduces the chromosome to one-half and is necessary before gametes are formed so the chromosome number will not double each generation. We shall consider all these processes in this chapter.

MITOSIS

When microscopes were greatly improved in the latter half of the nineteenth century, attention turned to detailed studies of cells. Stains were employed to make the cell parts more easily distinguishable from one another. In 1873 a number of different workers found that when basic stains were used threadlike or rodlike bodies could be seen in many cells. Since some of these stains were of bright colors, these bodies became known as chromosomes. Walther Flemming (see chapter 2) noted the relationship of the

chromosomes to cell division and called the process mitosis, derived from the Greek word *mitos*, "thread." These early workers did not see the process in living cells but deduced what happened from the stained preparations. Mitosis is divided into four stages (summarized below), each stage gradually merging into the next. Today we can see mitosis taking place in living cells through improved lighting techniques.

Prophase. The first sign of mitosis is the appearance of the chromosomes as long slender threads within the nucleus. A careful study shows that each chromosome is really double. The two parallel parts are known as **chromatids**. Sometime during the interphase that preceded mitosis the genes and chromosomes became duplicated, so they are already double when they enter prophase. Each double chromosome has a constricted area known as a **centromere**. As prophase progresses, the chromosomes become shorter and thicker by a system of coiling and recoiling. In late prophase the two chromatids of each chromosome may be somewhat separated and held together only by the centromere.

At the same time certain changes are taking place in the cytoplasm of the cell. If the cell is from a higher animal or some of the lower plants, a body known as a **centrosome** may be found near the outer boundary of the nucleus. Two small **centrioles** are within the centrosome. During prophase the centrioles separate and begin moving apart. A mass of fibers, the **spindle figure,** forms between them as they separate. Each **spindle fiber** is a microtubule of protein combined with a small amount of RNA to form a nucleoprotein. In addition **astral rays** of similar microtubules may extend out from the centrioles in the opposite direction from the spindle. Higher plants do not seem to have centrosomes, but the spindle figure appears across the cell in late prophase.

Metaphase. As the spindle figure envelops the chromosomes they begin to move into the region of the equator of the spindle, the portion equidistant from the two poles. When the chromosomes are thus positioned, metaphase begins. The centromeres form a line at the equator, a spindle fiber attached to each. The rest of the chromosomes may extend out in various directions, indicating that the attraction at the equator of the spindle is for the centromeres and not for the chromosomes as a whole. This assumption is further indicated by those cases where a part of a chromosome

Fig. 4–1. Plant mitosis, illustrated by cells of the onion root. Stages from left to right and top to bottom are: interphase, prophase, metaphase, anaphase, early telophase, and late telophase.

may become broken off from its centromere. Such a detached part will not move to the equator during metaphase and will not become included in the new nuclei that will be formed later; it will break up and be digested in the cytoplasm. Thus the genes it contained will be lost to the cell.

While the centromeres are aligned at the equator, they duplicate and are then pulled to the poles of the spindle by a shortening of the fibers. It appears as if these fibers are under tension, like a stretched rubber band, and as long as there is only one centromere

the tension is equal from both sides. Once a centromere has divided, however, the fiber tension pulls one to each pole. As the centromeres move they pull along the chromatids to which they are attached. Once the two chromatids separate into two units, each is called a chromosome. For example, a human somatic cell has 46 chromosomes during prophase and metaphase, although each is composed of two chromatids. When the chromatids become separated, however, there will be 92 single chromosomes in the cell.

Anaphase. As soon as the chromatids are completely separated, mitosis enters anaphase. This phase lasts only until the chromosomes reach the poles and become aggregated there. As seen in living cells this is rapid; as soon as the centromeres duplicate, the chromosomes zip right to the poles as would be expected if the fibers contract like elastic bands. The shape of the chromosomes at anaphase depends on the position of the centromere. If the centromere is median the chromosome will have a V shape; a sub-median location will give a J shape; and a terminal centromere will give a straight rod shape.

Telophase. Telophase is very much like prophase in reverse. The chromosomes, which became shortened and thickened by a coiling process during prophase, now become longer and thinner by uncoiling. The nuclear membrane that gradually broke up and disappeared during prophase now becomes reconstituted and new nuclei are established. The spindle figure that appeared during prophase disappears, although the centriole at the pole may duplicate and form a new centrosome. At the same time the actual division of the cell is taking place. In a typical plant cell a **cell plate** forms between the two daughter nuclei and gradually thickens to form a cell wall. In most animal cells a **cleavage furrow** develops on the outside of the cell, and this gradually constricts and pinches the cell in two. **Cytokinesis** is a word sometimes used to refer to the actual splitting of the cell into two parts, while mitosis is used to refer only to the changes within the cell before the splitting. Quite commonly, however, the word *mitosis* is used to refer to the entire process including the cell splitting.

Interphase. What happens to the chromosomes during interphase? At one time it was thought that they broke into pieces and ceased to exist as entities, then became reconstituted at the beginning of the next prophase. Such a conclusion was drawn because

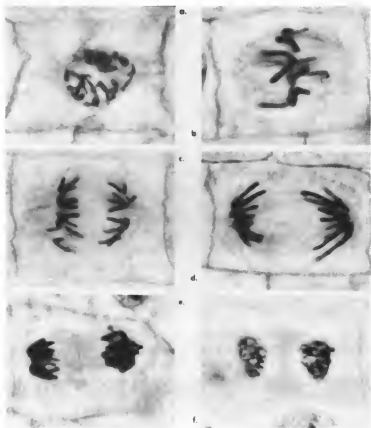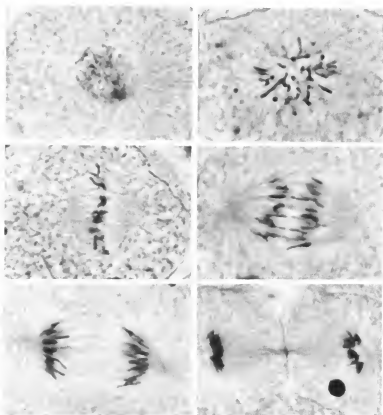*Fig. 4–2. Animal mitosis illustrated by cells of the whitefish. Stages from left to right and top to bottom are: interphase, prophase, metaphase, early anaphase, late anaphase, and telophase.*

chromosomes could not be seen during interphase with the microscopes available at that time. Now we know that the chromosomes retain their identity throughout interphase. They are extremely long and so thin that in most cases they can be seen only with advanced microscopic techniques. Some parts of the chromosomes may remain somewhat coiled and can be seen as what have been called chromatin granules.

STAGES OF INTERPHASE. Interphase may be divided into three stages.

G_1, *Growth Phase One.* When mitosis is completed the cell typi-
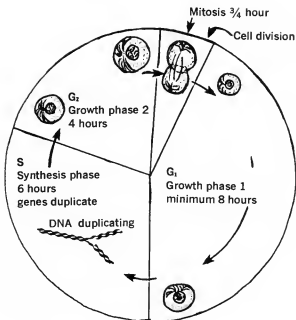
Fig. 4–3. The cell cycle. The time indicated is from human tissue culture cells under ideal growing conditions. (Reprinted by permission of Houghton Mifflin from Winchester, Genetics, 4th ed.)

cally enters into its most rapid growth period. Each daughter cell is only one-half of the size of the parent cell, and the genes begin coding messages for the production of new protoplasm.

S, Synthesis Phase. When the DNA begins replication the cell enters the S phase. Cell growth slows because replicating genes cannot also function in the production of new protoplasm. All chromosomes do not have DNA replication at the same time, however, so there will be some growth during this phase. For human chromosomes the shorter ones replicate first and the longer ones toward the end of the S phase.

G₂, Growth Phase Two. When DNA replication is completed the cell enters a second growth phase in which the genes can all function fully again. This is shorter than the first growth phase and terminates with the beginning of mitosis. Figure 4–4 shows the appearance of chromosomes during interphase and mitosis.

LENGTH OF INTERPHASE. The time between mitoses varies

greatly. The time interval ranges from several hours up to many years. As an example, let us consider human cells that have been removed from the body and are being grown in tissue culture under ideal conditions. Mitosis consumes about 45 minutes and G_1 will be about 8 hours. S will consume about 6 hours and G_2 will be about 4 hours. If there is variation in this schedule, it seems to be primarily in G_1. For instance, if growing conditions deteriorate, perhaps with a reduced food supply, G_1 might stretch out to 12 hours, several days, or even longer. Once the cell has entered the S phase, however, the rest of the interphase will still require only about 10 hours.
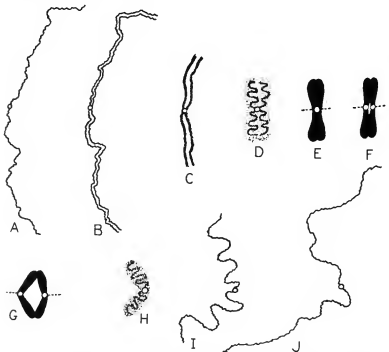
Fig. 4–4. Cycle of a single chromosome. A. As a single uncoiled strand in the G_1 of interphase. B. After the S phase the strand is duplicated, but still has only one centromere. C, D, E, and F. The chromosome becomes shorter and thicker by a system of double coiling in the prophase of mitosis. G. The two chromatics are pulled apart in the metaphase. H. In telophase the chromosome begins uncoiling until it reaches the interphase state in J.

You have cells in your skin that may go for weeks without entering the S phase and then mitosis. Should you injure your skin, however, the G_1 phase will be shortened as the cells grow faster and replace the injured tissue, and then the slower G_1 will return. Some of your cells will never again divide; they are said to be in G_0, growth zero. These include brain cells, certain kidney cells, and liver cells. If we can ever learn the secret of reactivating the S phase of these cells, we will have a possible way of restoring injured tissue in these vital organs. This is discussed more fully in chapter 14.

Cancer seems to result when there is a loss of control of the initiation of the S phase. Once a cell enters this phase, it goes on through mitosis and cell division if it continues to live. Cancer research today is directed at methods of preventing the initiation of the S phase. The body has natural controls that provide this initiation when new cells are needed and inhibit it when the need is satisfied. This control is lost, however, when cells become malignant.

TWINS AND OTHER MULTIPLE OFFSPRING

There is no better proof of the exactness of mitosis than the formation of identical twin animals. In the United States approximately one out of every 100 conceptions results in the birth of twins. About two-thirds of these are the result of fertilization of two eggs by two sperm, and the result is two individuals who are no more alike than brothers or sisters born at different times. In fact, they may even be opposite sexes. These are known as **fraternal** or **dizygotic twins** because they originated from two separate zygotes. The remaining one-third of the twins are **identical** or **monozygotic twins** because they start life as one zygote that then splits to give two complete individuals. Sometimes this splitting may occur at the two-cell stage, or it may even be after implantation within the uterus when the embryo consists of quite a number of cells. At any rate, the fact that two complete individuals can result from the splitting shows that mitosis has achieved an exact duplication of the genes present in the original zygote. Twins are of great interest to geneticists because they provide an excellent opportunity to study the effect of heredity and environment. Varia-
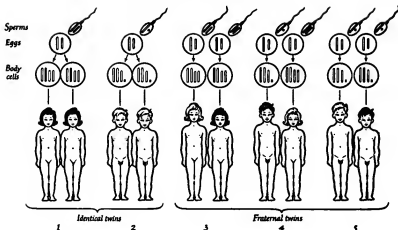
Fig. 4–5. Identical twins are always of the same sex and with the same inherited characteristics, while fraternal twins may differ in both sex and inherited characteristics.

tions in the characteristics of a pair of monozygotic twins must be due to environment because the two have identical genes. Dizygotic twins, on the other hand, will show variations due to both heredity and environment. Some such studies are described in chapter 18.

Twins can be artificially produced in experimental animals. A fertilized salamander egg (zygote) may undergo its first cleavage to produce two cells. If these are allowed to stay together, they will grow into one salamander; if the two are separated, each cell will form a complete salamander.

ASEXUAL PROPAGATION

Horticulturists have long used small parts of plants to initiate the development of entire plants. A twig placed in the ground will often put out roots and eventually grow into a tree that will bear the same kind of fruit as the one from which the twig was taken. Bulbs continue a choice variety of tulip, and underground stems permit iris fanciers to maintain a particular type of flower. Grafting of twigs or buds makes it possible to obtain desirable fruits of a predictable kind from the root stock of a hardy type that might produce undesirable fruits. This type of propagation is known as

cloning. All of this is possible because of the exactness of mitosis. No matter how many mitoses have taken place since the formation of a zygote, the cells will still have the gene combination present in that zygote.

There has even been preliminary success in cloning of higher animals. In 1966 J. B. Gurdon at Oxford University accomplished cloning in frogs. He radiated an egg from one species of frog with ultraviolet light to destroy the nucleus. Then with a micropipette he removed the nucleus from a cell of the intestine of another kind of frog and injected it into the enucleated egg. This egg began to undergo cleavage, and in time a frog was produced with characteristics of the one from which the nucleus was taken. This gives striking proof that mitosis results in duplication of the genes even though the cytoplasm may differentiate considerably. Such a process could theoretically be carried out with human beings. In human cloning the nucleus from one of the cells of an adult person would be injected into an enucleated egg and this implanted in the uterus of a woman. The child she bore would be an identical twin of the nucleus donor. Some might like the idea of human cloning; we could produce many duplicates of some popular sex goddess, star athletes, great artists, outstanding scientists, or those who achieve greatness in other fields.

THE CHROMOSOME NUMBER

All members of the same species typically have the same chromosome number. For the human species this is 46, which is one of the higher numbers, although certain species of monkeys outnumber us. The size of chromosomes is variable, however, so the number is not necessarily an indication of the number of genes. A crayfish, for instance, has about 200, but each is only a tiny dashlike body, so the total amount of DNA in a crayfish cell is actually much less than that in man. A truer estimate of the number of genes is a measure of the amount of DNA in a cell. Man has about 8.6×10^{-12} gram in a typical somatic cell, such as a kidney cell, but a domestic chicken has only 2.5×10^{-12} gram of DNA in a somatic cell. A snail has only 1.34×10^{-12} gram per somatic cell. Since genes will probably be about the same length in all organisms, we can conclude that man has over three times as many genes as a

TABLE 4–1
DIPLOID CHROMOSOME NUMBER OF CERTAIN ORGANISMS

Ascaris (roundworm)	4
Drosophila melanogaster (fruit fly)	8
Garden pea	14
Onion	16
Corn	20
Opossum	22
Honeybee	32
Domestic swine (hogs)	38
Mouse	40
Man	46
Potato	48
Monkey (*Cebus*)	54
Crayfish	200

chicken and about six times as many as a snail. Table 4–1 shows the chromosome numbers of a few species of plants and animals.

In sexual reproduction there would seem to be a problem with relation to the chromosome number. A new individual arises from the union of two sex cells, and if each sex cell carried a full complement of genes and chromosomes, there would be a doubling of these each generation. This, of course, does not happen; a child will have 46 chromosomes just like its parents, so something must take place to reduce the chromosome number in the gametes before they unite. What occurs is two successive cell divisions accompanied by only one gene and chromosome duplication, a process known as *meiosis*.

MEIOSIS IN ANIMALS

Meiosis is a word taken from the Greek *meioun*, "to lessen." It refers to two processes, each somewhat like mitosis, but differing so as to reduce the chromosome number to one-half. Somatic cells contain two of each kind of chromosome; the number of chromosomes in this double set is thus known as the **diploid number.** For each chromosome of a certain length and point of centromere

attachment there will be a mate of the same kind in the cell. These paired chromosomes carry homologous genes at the same points on each. For example, suppose there is a gene that influences the degree of pigmentation of the iris of the human eye, located near the terminal end of chromosome 12. There will also be a gene that affects this same trait at the same location on the homologous chromosome. These two genes may be alike, both for the same degree of pigmentation, or they may be different for different degrees of pigmentation. Both, however, are for the same trait. Hence we think of the human chromosome complement as 23 pairs of chromosomes.

Let us first follow the process of meiosis as it takes place in the testes of a man.

Spermatogenesis. Within the human testes there are many tiny tubules, each about the diameter of a coarse sewing thread. A microscopic study of a cross section of one of these **seminiferous tubules** reveals an outer **germinal epithelium** made of cells known as **spermatogonia.** Let us follow one of these. It divides by mitosis and produces two cells; one stays in place and the other migrates inward and becomes a **primary spermatocyte.** The latter cell undergoes the S stage in interphase as if in preparation for mitosis, but as the chromosomes shorten and become visible in early prophase a difference is apparent: The chromosomes are paired. Since each is also double, each pair consists of four **chromatids** known as a **tetrad.**

The tetrads line up at the equator of the spindle at metaphase. There are already two centromeres; hence there is no centromere duplication. The paired chromosomes separate to opposite poles of the spindle so that the cell divides to give two **secondary spermatocytes.** Since each of these has 23 chromosomes, reduction in chromosome number has been accomplished, but each chromosome has two chromatids. Each secondary spermatocyte now enters the second meiosis (meiosis II), but there is no interphase S phase. The genes have already duplicated in the S phase preceding the first meiosis. The prophase chromosomes of the second meiosis are **dyads** that look very much like those in mitosis, only there are just half as many of them. These line up on the spindle, the centromeres duplicate, and 23 single chromosomes are dragged to each pole by their centromeres. The cell divides to give two **spermatids,** each with 23 single chromosomes, the **haploid,** or **monoploid,** number, and the reduction has been completed.

SPERMATOGENESIS   OOGENESIS
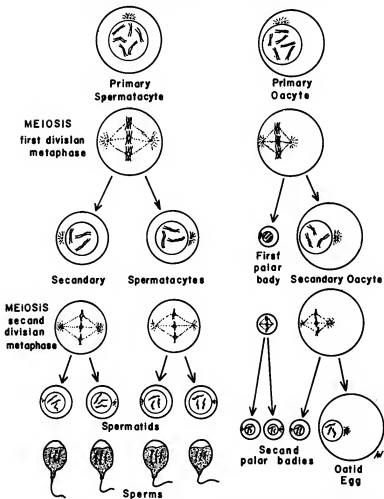
Fig. 4–6. The formation of sperm and eggs through meiosis. Through two cell divisions there is only one division of the chromosome. The diploid number shown here is 6; there would be 46 in human cells.

Thus we see that in meiosis there are two cell divisions but only one gene duplication, one chromosome duplication, and one centromere duplication. Everything happens in the two parts of meiosis as happens in the one part of mitosis, except that there are two cell divisions in meiosis.

Spermiogenesis. Each spermatid is converted into a sperm by spermiogenesis. There is an elimination of the excess cytoplasm and the formation of a tail for swimming. A region of the cell known as the golgi apparatus accumulates at one part of the spermatid. This forms the **acrosome**, which will be at the front of the head of the sperm. It is rich in enzymes that will enable it to penetrate the barriers to the egg. **Mitochondria**, the energy-producing bodies of the cell, accumulate at the opposite side of the cell. These will be in the middle piece of the sperm and will furnish the energy required for the wiggling movements of the tail. The tail grows out from this region, and blobs of excess cytoplasm pass off down the tail as it lengthens. The end product is a sperm, a body that carries only those parts necessary to get the genes of the male to the egg. Just enough food material is stored in the middle piece along with the mitochondria to allow the sperm to swim actively for several hours at room temperature. Within a woman's body they remain functional for several days because they apparently absorb some food from her reproductive tract. Sperm can be refrigerated, however; this slows their movements, and they will retain their activity for a week or longer. If quickly frozen and kept at the temperature of liquid nitrogen, which is $-196°C$, they cease activity and can retain their potency for years.

Fig. 4–7. Living human sperm. In the top photograph, the head is flat, while the lower photograph shows the head on its side.
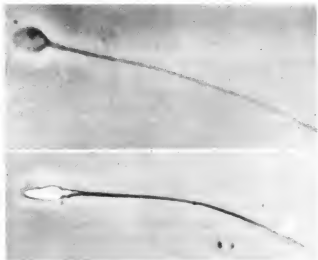
Cattle breeders maintain frozen sperm banks for use in fertilizing cows whenever desired. The practice has even been extended to human semen, and most large cities now have one or more human sperm banks where a man can deposit some of his semen for possible future use. This is sometimes called fertility insurance, because a man can still father children after having the sterilizing operation called **vasectomy** as a means of birth control.

Oogenesis. Human oogenesis can be used to illustrate egg formation in mammals. The germinal epithelium of a woman lies at the outer edge of her ovaries. This contains the **oogonia,** which can multiply by mitosis and then produce **primary oocytes.** A primary oocyte will go through the two divisions of meiosis, but there is one important difference when the process is compared to spermatogenesis: The spindle figure forms near the outer boundary of the cell and the cell cleavage is unequal, giving one large **secondary oocyte** and one **polar body** at the first meiosis. Cell cleavage is also unequal at the second meiosis, giving one **ootid** and a second polar body. The polar bodies play no part in reproduction and seem to serve only to receive the excess chromosomes so that the ootid will have only the haploid set of chromosomes. The ootid becomes an egg without much further change.

Strange to say, the first meiosis in a woman may take place as early as the seventh month of embryonic life, but the second meiosis takes place at the time of ovulation, which may be from 12 to 45 years later. This long association of the dyads in between the first and second meiosis may cause them to adhere during the second meiosis so that both chromosomes of a pair go to one pole. If the chromosome were chromosome 21, for instance, one cell would get two 21s while the other would get none. See chapter 16 for a discussion of the abnormalities that may result. In some animals the first polar body undergoes a second meiosis to give two more polar bodies, the end result being one egg and three polar bodies.

FERTILIZATION

The union of the haploid sperm and the haploid egg restores the diploid chromosome number. We can illustrate the process in human reproduction. An egg is released from one of a woman's

two ovaries once every 28 days on the average. This is known as **ovulation**. This egg passes into the Fallopian tube, which leads down to the uterus. The egg seems to be susceptible to fertilization for only about a day after ovulation. Normally this occurs as the egg travels down the Fallopian tube. Sperm surround the egg, which is encased in a corona of small follicle cells. The enzymes in the acrosome of the sperm dissolve away the cement that holds these follicle cells together, and eventually one sperm head contacts the surface of the egg. This seems to trigger a chain reaction that travels around the surface of the egg and prevents more sperm from becoming attached. The head and middle piece of the sperm are then engulfed by the egg, and fertilization has been accomplished. Within about 30 hours the first mitosis takes place and a new embryo has begun its existence. By the time it reaches the uterus about five or six days later, it is a ball of cells. It soon becomes implanted in the uterine wall.

GENE ASSORTMENT IN MEIOSIS

The assortment of chromosomes in meiosis is like the shuffling and dealing of cards. As the chromosome pairs line up on the metaphase plate the placement of maternal and paternal chromosomes is random. As a result, a gamete will receive about half of the paternal chromosomes and about half of the maternal chromosomes, but they will be a different assortment for the different gametes. The chance that any two gametes will receive exactly the same chromosome assortment is only about one in 8.4 million ($\frac{1}{2}^{23}$). When both gametes are considered, the chance of two children of the same parents receiving the same combination of chromosomes is at the astronomical figure of only about one in 70.5 million, identical twins excepted. Even this figure is far too frequent because paired chromosomes can exchange segments with one another to give chromosomes that are part paternal and part maternal, a process known as crossing-over. Thus it is easily seen how sexual reproduction makes possible a high degree of variety. Even in those species, such as parasitic worms and many fish, that lay eggs by the millions, there will be no two offspring exactly alike.
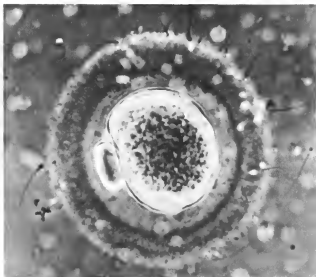
Fig. 4–8. Sperm penetrating the corona surrounding a living human egg. Note the second polar body at the left. (Courtesy Landrum Shettles.)

HYBRIDIZATION

Sometimes closely related species may be crossed and hybrids obtained. Such hybrids, however, are typically sterile because the chromosomes do not match during meiosis and cannot produce gametes with a viable number of chromosomes. For example, the red fox has 34 chromosomes while the arctic fox has 52. When the two are brought together, there is sufficient sexual attraction to result in mating. Each of the hybrids will have 43 chromosomes. When the time for gamete production comes, however, it is obvious that there cannot be a perfect pairing (synapsis) of chromosomes. For one thing, the diploid number is odd, and one chromosome would have no mate. For another, many of the genes will be so different that there will not be proper pairing and any spermatids or ootids formed would have combinations that would not be viable. This topic is discussed more fully in chapter 16, and methods of obtaining fertile interspecific hybrids in plants are described.

PARTHENOGENESIS

An egg contains a complete haploid set of chromosomes, which is all that is needed to form a complete individual. In most cases, however, the egg will not begin cleavage without the stimulation of fertilization. It seems likely that some enzyme in the sperm head sets forth a chain reaction of enzyme release within the egg which initiates mitosis. In some instances this stimulation by the sperm is not necessary, and the infertile egg undergoes mitotic divisions and forms a new life. This is called parthenogenesis. Eggs laid by the queen honeybee will, if unfertilized, develop into male drones with the haploid chromosome number. The female aphids that feed on many garden plants have several generations of females during the summer through parthenogenesis, then produce males in the fall by sexual reproduction. The eggs of most animals, however, never start development without fertilization.

In some cases eggs can be artificially stimulated into development. When sea urchin eggs are placed in very strong salt water they begin cleavage and produce embryos. Frog eggs pricked with a fine needle dipped in frog blood have started cleavage. Even unfertilized rabbit eggs have reportedly been so stimulated and, when transplanted into virgin females, produced normal offspring. Biologists at Beltsville, Maryland, found a breed of turkeys that laid eggs which would sometimes hatch when incubated even though the females never had contact with tom turkeys.

Parthenogenesis has often been claimed by women who would prefer not to admit to sexual intercourse, but most such claims have been disproved by simple genetic tests, which show that the babies born had traits that would have had to come from someone besides the mother. A check of the blood types and other blood characteristics is usually sufficient to accomplish this; if this is not possible, skin grafts can be attempted. A mother should be able to accept a graft from her parthenogenic child because that child's tissues could not have any proteins not possessed by her. So far, no such compatibility has been found, so a father must have provided genes for some of the child's proteins.

MEIOSIS IN PLANTS

In plants with sexual reproduction meiosis reduces the chromosome number in a manner quite similar to that in animals. After meiosis in plants, however, the haploid cells duplicate a number of times by mitosis before gametes are formed. In the lower plants this duplication is extensive, so that much of the plant body consists of haploid cells; but with increasing complexity of the plants there is a gradual shift to a predominant diploid phase of the life cycle.

Liverworts, Mosses, and Ferns. Figure 4–9 shows the life cycles of these plants. You can see that the liverworts are somewhat like a double forked leaf. This body, called a thallus, grows flat on the ground in damp places. The entire plant that can be seen with the naked eye has haploid cells. Male and female reproductive organs grow up from the thallus and produce sperm and eggs. When a sperm fertilizes an egg, the diploid zygote undergoes several mitotic divisions, then undergoes meiosis and produces haploid spores. Each of these can grow into a haploid thallus. The
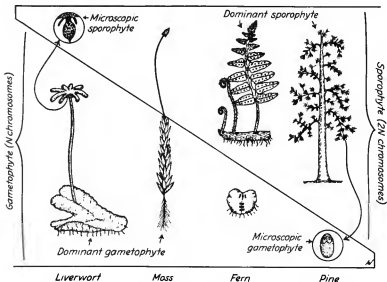

Fig. 4–9. Diagram showing the proportion of the plant given over to haploid and to diploid tissue in four different plant groups. (Reprinted by permission of Houghton Mifflin from Winchester, Genetics, 2d ed.)

haploid tissue is known as the **gametophyte,** while the tiny diploid body that produces the spores is the **sporophyte.**

In mosses the gametophyte is still the predominant form in the life cycle, although the sporophyte is larger. The sporophyte grows up as a slender stem from the top of a female gametophyte after fertilization has occurred. Haploid spores are produced by meiosis at the upper tip of this sporophyte.

In ferns there is a predominant diploid sporophyte. The fronds, underground stems, and roots are all diploid. Meiosis takes place on the sori, which are underneath the fronds, and haploid spores are produced. These may be spread by wind, and each can grow into a small thallus, which looks like a small liverwort. This is the haploid gametophyte. Gametes are produced on the gametophyte, and a new sporophyte grows up from the zygote after fertilization.

Seed Plants. In the higher plants, or seed plants, the gametophyte has been reduced to a microscopic size. Most seed plants have either flowers or cones, and meiosis takes place in these structures. There follow a few mitotic divisions to give a tiny gametophyte. The male gametophyte, consisting only of the pollen grain, is usually carried to the female gametophyte by insects or wind. A male nucleus unites with a female nucleus and the diploid number of chromosomes is restored. Then mitotic divisions produce a young embryo enclosed in a hard covering containing nutrients; this is known as the seed.

PROBLEMS

1. In what respects is telophase a reversal of prophase and how is it different?

2. The haploid chromosome number of a certain fruit fly is four. How many chromosomes would you expect to find in each of the following cells: prophase of mitosis, anaphase of mitosis, prophase of the first meiosis, telophase of the second meiosis, prophase of the second meiosis?

3. A certain chemical, colchicine, prevents the formation of spindle fibers. What effect would this chemical have if applied to a cell during prophase?

4. If a certain worm has 40,000 genes as its haploid number, how many genes would you expect in the following cells: G_2 of

interphase preceding mitosis, G_1 of a secondary oocyte, anaphase of the first meiosis, telophase of second meiosis, a spermatid?

5. Some cases of parthenogenesis come about because the second polar body reenters the egg to fertilize it and give a diploid zygote. Would the offspring that result be exactly like the mother genetically? Explain.

6. There are two of each kind of gene and two of each kind of chromosome in somatic cells of animals and higher plants. What problem would arise if there were only one kind of each in these cells?

7. The hybrid produced from matings between two closely related species of animals is usually sterile. Explain why.

8. Outside of the fact that the diploid state is necessary for sexual reproduction, what advantage might accrue to a higher plant or animal as a result of the presence of two genes for each trait?

5. THE MONOHYBRID CROSS

Gregor Mendel discovered the basic methods of transmission of inherited characteristics (see chapter 2), often referred to as Mendelian inheritance. He first studied the transmission of single traits in garden peas by cross-pollinating plants that differed primarily with respect to one trait. This became known as a monohybrid cross.

BASIC PRINCIPLES OF MONOHYBRID INHERITANCE

One of Mendel's monohybrid crosses involved the color of flowers. He placed pollen from a purple flower on the pistil of a white flower and obtained seed that grew into plants with all purple flowers. When the pollen was taken from a white flower and placed on the pistil of a purple flower, the results were the same, indicating that the sex of the parent had nothing to do with the transmission mechanism. When the first-generation hybrids were allowed to self-pollinate, both purple and white flowers were observed in the second generation. The ratio was approximately 3 purple: 1 white. Mendel applied his keen analytical mind to the results and came up with a remarkably accurate hypothesis as to how genetic traits are inherited.

Dominance and Recessiveness. Mendel reasoned that there must be two "factors" for each trait in the plants, but the reproductive bodies, pollen and ovules, would receive only one of the two. When two reproductive bodies combined to form a seed, the plant that came from it would again have the two factors. We now use the word *gene* instead of factor, but the principle has proved to be essentially correct. Mendel reasoned further that when the two factors in a plant differed, one would be dominant and the other
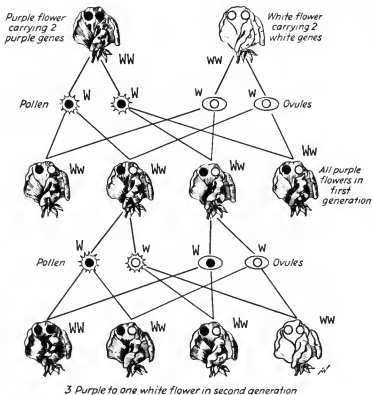
Fig. 5–1. One of Mendel's monohybrid crosses with garden peas. From such results, he reasoned out the method of transmission of single traits. (Reprinted by permission of Houghton Mifflin from Winchester, Genetics, 4th ed.)

recessive. The dominant factor would be expressed while the recessive would be suppressed, but the recessive trait could appear in later generations when two recessive factors came together. Continued study has verified these deductions by Mendel, although we now know that an inherited trait may be the result of the action of more than one pair of genes and that some gene pairs both express themselves, as we shall learn later in this chapter.

The principle of assortment of genes (factors) during the formation of reproductive cells is one of Mendel's major contributions to modern genetics. When two varieties of a factor for a particular characteristic are carried by an individual, they are so segregated during the formation of reproductive cells that about half of these

cells will carry one variety and the other half will carry the other variety.

Gene Symbols. Mendel recognized the necessity of using symbols for the factors, or genes, as we shall now call them. He decided to use the same basic letter for both genes of a pair to avoid the confusion that would arise if different letters were used, especially when several gene pairs were being considered at one time. He used the capital form of a letter for the dominant gene and the lowercase form of the same letter for the recessive alternate gene. He also used the first letter of the trait that deviated from the more common of the two traits. Since white flowers were less common than purple flowers, he chose w as the symbol for the gene for white. (In his native language, as in English, this was the first letter of the word for white.) The alternate gene for purple then became W. We still use this system with certain modifications.

Although most deviations from the common condition are due to recessive genes, there are some that result from dominant genes. One of these is Huntington's disease, which brings about mental and physical deterioration beginning at about age 30. Since this disease is certainly not the most common condition, we use H as the symbol for the gene involved and h for the gene that does not cause it. When dealing with a trait about which there is doubt as to which is more common, use the first letter of the recessive. Never use N or n for normal; if the trait is normal, it cannot be the less common of two alternatives. Also, avoid the common misconception that dominant genes are always the most common. It is the gene frequency in a population rather than its dominance or recessiveness that determines how many people express a trait. In Norway most of the people you see have blue eyes, yet blue eye color is due to a recessive gene. In southern Italy most people have brown eyes because most of the genes in this population are the dominant one responsible for melanin deposit in the iris.

Geneticists studying many traits in a single species may use two or more letters as single gene symbols to avoid having the same letter for different genes. For instance, in the fruit fly, *Drosophila,* a recessive gene causes the eyes to be vermilion in color, and the letter v was chosen to represent it. When a recessive gene responsible for vestigial wings was found, vg was used to designate it. Some who work primarily with *Drosophila* find it convenient to use a plus sign for the normal alternate genes. A fly with normal wings

Fig. 5–2. Fruit fly with vestigial wings. This trait results when a fly is homozygous for a recessive gene vg/vg.

that carries the gene for vestigial wings would thus be represented as $vg/+$ or vg/vg^+. The diagonal line represents the chromosome and shows that the genes lie opposite one another in meiosis.

Since there is no dominance and recessiveness in haploid organisms, the microbial geneticists have devised modified designations. For instance, a gene in some bacteria produces an enzyme that can synthesize the amino acid methionine. The symbol for this gene is met^+, and the symbol for its alternate that cannot produce the enzyme in functional form is met^-.

Terminology. Mendel's method of designating generations is also still in use today. The plants involved in the first cross-pollination he labeled the P_1, or first parental generation. The offspring of these parents he called the F_1, or first filial generation, the offspring of the F_1 he called the F_2, and so on.

When the offspring of the same parents undergo self-fertilization, the cross is called an *inter se cross*. When offspring are bred back to one of the parents, the cross is called a **backcross**. The term **testcross** is used when we breed an individual with a dominant phenotype to one with the recessive phenotype in order to determine the genotype of the dominant individual. Figure 5–3 shows how a solid-colored cocker spaniel dog may be tested to determine if he carries the recessive gene for particolored (spotted).

We need terms to differentiate between individuals who carry two dominant genes for a particular trait and those who carry one

THE TESTCROSS
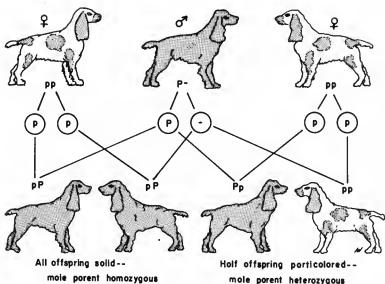
Fig. 5–3. The testcross in cocker spaniel dogs. The solid-colored male is bred to particolored females to determine if he carries the recessive gene.

dominant and one recessive. If the trait is fully dominant, the two individuals will look alike, at least for that trait, but their offspring can be quite different. Those with two genes alike are called **homozygous** for that gene pair, while those who have one gene of each kind are **heterozygous.** All individuals who show the effect of a recessive gene must be homozygous, because they cannot carry the dominant alternate without its being expressed.

Alternative pairs of genes for the same trait are called **alleles.** For example, the gene that produces the human enzyme for melanin production, *A,* is an allele of its alternate gene, *a,* for albinism, which does not produce this enzyme. Alleles always occupy the same position on the paired chromosomes in meiosis; in fact, the attraction of allelic genes for one another causes the chromosomes to synapse in meiosis.

The term **genotype** refers to the type of genes in an individual and **phenotype** to the expression of the genes. For instance, a person with a genotype of either *Aa* or *AA* would have a pheno-
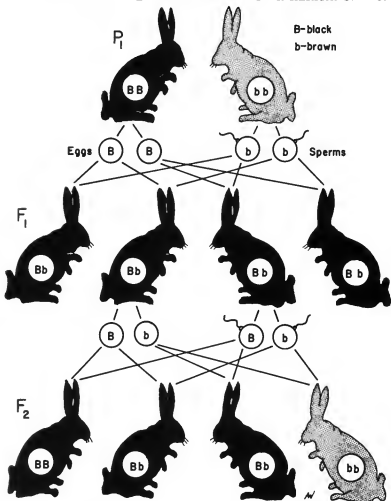
Fig. 5-4. A monohybrid cross between black and brown rabbits showing manner of choosing gene symbols and designating generations.

type of normal pigmentation (nonalbinism), whereas a person with the genotype aa will have the phenotype of albinism.

Determining Genetic Ratios. We can determine the ratio of both genotype and phenotype expected from a given genetic cross. As 'an example, let us consider a cross between a black and a brown rabbit. The gene for black is dominant while its recessive

allele is for a brown coat. The following diagram shows two generations:

B—black

b—brown

P_1 BB × bb

gametes B B b b

F_1 Bb × Bb Phenotype: all black
                          (*inter se* cross)

gametes B b B b
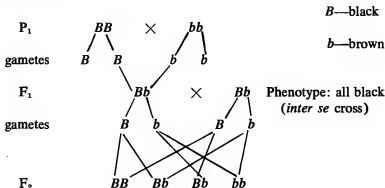
F_2 BB Bb Bb bb

Phenotypic ratio—3 black:1 brown

Some prefer to use the checkerboard method of obtaining the second-generation genotype and phenotype. This was first devised by R. C. Punnett and is sometimes called the Punnett square.

Sperm

		B	b
Eggs	B	BB	Bb
	b	Bb	bb

Phenotypic ratio—3 black:1 brown

Geneticists tend to do much of the calculation in their heads and may write out the cross as

$$Bb \times Bb = BB + 2Bb + bb \text{ (3 black:1 brown)}$$

When there is only one kind of gamete from an individual, you can save time by using only one of these gametes in the diagram. For instance, to predict the ratio of the children from a heterozygous, normally pigmented man and an albino woman, you could use the following representation:

Phenotypic ratio—1 normal:1 albino

DIFFERENCES IN GENE EXPRESSION

One gene of a pair of alleles is not always dominant. Both of the alleles may be expressed to some degree.

Intermediate Inheritance. When each of two allelic genes is partially expressed, we have what is called intermediate inheritance or, as some prefer to call it, an absence of dominance. When a red short-horned bull is mated with a white cow, the calf will be roan, a color about halfway between red and white. When two roans are crossed together, we get red, roan, and white offspring in a 1:2:1 ratio. Thus it is apparent that both the gene for red and the gene for white are partially expressed in heterozygous animals. In this kind of inheritance we cannot use capital and small letters as gene symbols because neither gene is dominant. However, we can still adhere to our principle of using the same letter for allelic genes by having a basic capital letter stand for both genes and then distinguishing between them by adding superscripts. Thus, in the above example we can use C for color; the gene for red would be C^R while the gene for white would be C^W. A cross between two roan cattle could be represented as

$$C^R C^W \times C^R C^W = C^R C^R + 2\ C^R C^W + C^W C^W$$
$$\text{(1 red:2 roan:1 white)}$$

A breeder of chickens may wish to produce blue Andalusians. If he crosses blues together, however, he gets only half blue while the remainder will be white and black in equal proportions. Obviously this is a case of intermediate inheritance. The blue is heterozygous for the genes for white and black; the black is actually a very dark blue. To get all blue offspring, the breeder should keep white hens and black roosters or the reverse sexes.

Manx cats have short tails. When two such cats are bred to-

INTERMEDIATE INHERITANCE
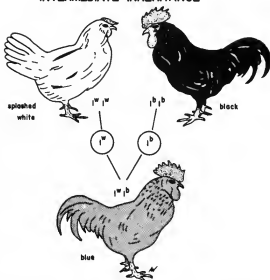
Fig. 5–5. Intermediate inheritance in the domestic fowl. The Andalusian blue is a heterozygous expression of the genes for splashed white and black.

gether, half the offspring will have the short tails, about one-fourth will have long tails, and the other fourth will have no tails at all. Breeders supply the demand for Manx cats by breeding long-tailed cats with no-tailed cats because they know that this is another case of intermediate inheritance.

Codominant Inheritance. In some cases both genes of an allelic pair are fully expressed and may be called codominant. The genes responsible for the A and B antigens of the human blood are examples. One gene codes the production of antigen A, which is found in the plasma membrane around the red blood cells. An allele codes for antigen B. A person heterozygous for the two alleles will have type AB blood, in which both genes are fully expressed. The genetics of blood types is considered more fully in chapter 11.

Incomplete Dominance. In many cases where we have assumed that a certain gene is dominant we have found upon close examination that there is a detectable difference between the homozygous dominant and the heterozygous dominant. In *Drosophila*, for

instance, there is a recessive gene for sepia-colored eyes. The dominant allele contributes to the formation of the pigment in the wild-type red eye. Now the eyes of homozygous dominant and heterozygous dominant appear equally red to the observer, even when viewed under a microscope. However, if the eye pigments are separated by chromatography, it is evident that there is less of a certain fluorescent pteridine pigment in the heterozygote. With tests such as this it is often possible to detect the dominant carriers of a recessive gene.

Many genes exert their influence through enzymes that they code for production. Tay-Sachs disease is a horrible affliction that appears in children who are homozygous for a certain recessive gene. This gene cannot produce the normal enzyme needed for metabolism of fatty substances around the nerves. A baby homozygous for this gene is normal at birth, but beginning at about five or six months of age the accumulation of fatty deposits around the nerves brings about a gradual loss of mental and physical abilities and death within a few years after birth. Heterozygous carriers of this gene can be recognized by analyzing their blood for the enzyme involved. Even though they show no symptoms of the disease, carriers of this gene will have less of the enzyme than noncarriers.

Phenylketonuria (PKU) occurs in individuals homozygous for a recessive gene that cannot produce a liver enzyme needed to break down an amino acid, phenylalanine. The resulting accumulation of this amino acid in the body causes improper brain development in a child. One normal gene can produce all of the enzyme needed, so the heterozygote is just as normal mentally as the homozygote. The two can be distinguished, however, by creating stress. Extra quantities of phenylalanine are given in a glass of water. Those with two normal genes will be able to break down this extra amino acid much faster than those with only one gene for the enzyme production. Blood tests made after administering the extra phenylalanine will often reveal the carriers because it takes them longer to bring the amino acid level back to normal.

Level of Gene Expression. When we speak of dominance and recessiveness, we must think in terms of level of expression. On the gene level there is always a difference between the heterozygote and the homozygote. On the cellular level there is very likely to be a difference, but on the organism level there may be none. The gene for sickle-cell anemia produces a type of hemoglobin which

differs from that produced by its normal allele. Individuals homozygous for the gene have sickle-shaped red blood cells that do not carry oxygen well. The result is severe anemia, which often causes early death. On the organism level this gene may appear recessive, since the heterozygous carriers usually do not show the anemia. An electrophoretic separation of the hemoglobin, however, will reveal a difference. Two separate types of hemoglobin can be detected, one normal and the other a deviation from normal. On the cellular level, therefore, the inheritance would be considered intermediate. The difference can also be detected on the organism level under stress conditions. When people who are heterozygous go to a high altitude, the lowered concentration of oxygen in the air will cause some cells to sickle and anemia may result. Hence dominance and recessiveness are relative terms.

Explanation of Dominance and Recessiveness. Why are some genes dominant and some recessive? Why are genes for normal development most often dominant over those for abnormal development? Why do some genes have an intermediate or codominant expression when heterozygous? A study of the method of gene action helps to answer these questions.

Genes code the production of proteins in cells. Some of these are **structural proteins** that add to the protoplasm and therefore contribute to cellular growth. Others are **functional proteins**, primarily enzymes, which stimulate chemical reactions in the cell. Genes that produce normal enzymes are generally dominant while their alleles that either do not produce the enzyme or produce it in a defective form are recessive. This happens because the capacity to produce an enzyme is usually at least twice that needed under normal conditions. While the demands for the enzyme vary, this extra capacity can usually supply all that is needed. In the heterozygous individual the one dominant gene works twice as hard as when two are present. An analogy would be the use of two horses or one to pull a wagon. One horse is able to pull a normal load, although he must work twice as hard as when two are pulling. Pulling a heavy load up a steep hill, however, can bring out a difference. Likewise, under stress conditions, the difference between the homozygote and heterozygote can be detected. Sometimes, even under normal conditions, the demand for the enzyme can be so great that the heterozygote shows an intermediate expression.

Genes that code structural proteins usually have an effect that is

intermediate or codominant on the cellular level at least. We have already learned that a person heterozygous for the gene for sickle-cell anemia will have both normal and abnormal hemoglobin in the red blood cells. Also, a person heterozygous for the alleles for the A and B blood antigens will have both of these. A few deviant alleles of normal genes that produce structural proteins are dominant on the organism level. About one person in each 10,000 carries the dominant gene for **Huntington's disease.** This gene codes the production of a defective type of protein in the basal ganglia of the cerebral cortex of the brain. The normal allele in a heterozygous person can produce sufficient normal protein during childhood and young adulthood to prevent any abnormalities. As anabolism slows with increasing age, however, the cortex of the brain shrinks and there is a loss of mental and physical capabilities. There is an uncontrollable shaking of the hands and other body parts (chorea) that becomes progressively worse, and the mental deterioration continues until the person usually ends life in an institution. Hence the gene is classified as dominant on the organism level as well as the cellular level.

LETHAL GENES

Some genes so alter the normal phenotype as to lower the chance of survival. In the laboratory it is possible to maintain stocks of flies that are homozygous for a recessive gene for vestigial wings, that is, wings reduced to mere stumps. In nature such a phenotype would so lower the chance for survival that most of the flies expressing the trait would not live very long after emerging from the pupal case. Hence this would be a gene of very low viability. Genes that so lower viability that practically all individuals expressing them die are said to be lethal genes.

Time of Expression of Lethal Genes. Some genes may interfere with the first division of the zygote and cause death shortly after fertilization. Others may prevent survival of the embryo when it is a microscopic ball of cells. Still others may not take effect until the embryo is fully formed. Many human babies die shortly after birth because of lethal genes that prevent the normal functioning of the lungs, kidneys, or heart. The gene for albinism in green plants does not interfere with embryonic growth or the

sprouting of the seed, but when the seedling is several inches tall it will die because it cannot manufacture food.

Frequency of Lethal Genes. Most lethal genes are recessive. Dominant lethals may arise by mutation, but they are eliminated in the first generation. Recessive lethals, however, can be carried in the heterozygous condition for many generations. It is estimated that each person carries about four such recessive lethals, but because there are so many different kinds, most couples do not carry the same ones. When they do, about one-fourth of the conceptions terminate in death at some time in development. Many spontaneous abortions are the result of such lethals. The frequency of such deaths goes up when the parents are related because they are more likely to carry the same lethals.

Intermediate Lethals. Some lethal genes have a phenotypic expression that is viable in the heterozygous condition but cause death when homozygous. A classical illustration is found in cattle. In a certain breed in England there is a gene that, when homozygous, produces a bulldog calf. Such a calf has very short legs, a shortened muzzle that gives it the appearance of a bulldog, and other deformities that cause death at, or shortly after, birth. When heterozygous calves are born, they survive but have shortened legs and other expressions of the gene; these are known as **Dexter cattle. Kerry cattle** are those homozygous for the allele of the lethal; they have normal legs and other characteristics. A monohybrid cross between two Dexters gives offspring in a ratio of 1 Kerry:2 Dexter:1 bulldog.

In the case of genes that cause death before birth or hatching, the ratio obtained from crosses of two with the intermediate phenotype will be 1:2. In *Drosophila* a certain gene, when heterozygous, causes **Dichaete wings.** The wings are held out to the side instead of over the body, and the bristles on the body are shorter than normal. A cross of two flies with such wings gives a ratio of 1 normal:2 Dichaete. One-fourth of the pupae fail to live to the time of emergence so are not represented in the ratio of live flies produced.

No doubt many of the human genes that cause some abnormality when heterozygous are of this nature. One such gene causes a shortening of the fingers; there appear to be two joints instead of three because the middle joint is shortened and fused to one of the other joints. The condition is known as **brachyphalangy.** It was thought to result from a dominant gene until a marriage was found

between two individuals with the short fingers. They had four children, one with normal fingers, two with brachyphalangy, and one without any fingers or toes and with other skeletal defects who was unable to survive. This was the 1:2:1 ratio expected from intermediate lethals.

GENES IN HAPLOID ORGANISMS

There are many small organisms that are haploid, that is, they have only one set of genes, at least during the greater part of their life cycle. In these organisms there is no such thing as dominance, recessiveness, or intermediate relationships of genes. All the genes that are present in an organism are expressed. This makes such organisms quite valuable in mutation studies because any mutations that appear will be expressed in the first generation. Mutation studies with haploid organisms will be considered further in chapter 15.

PROBLEMS

1. In domestic poultry some chickens have a rose comb (one with multiple divisions), and others have a single comb. One of these traits results from a dominant gene and the other from a recessive allele. Tell how you would determine which trait is dominant and which is recessive.

2. Assume that you find the rose comb is dominant. Show the results of a cross between a homozygous rose-combed rooster and a single-combed hen. Carry to the F_2.

3. Some persons have free-hanging earlobes while others have earlobes attached directly to the head. Assume that attached earlobes are recessive. Show the types of children to be expected from a marriage between a woman with attached earlobes and a man with free-hanging earlobes who had a mother with attached earlobes. Include full genotypes and phenotypes of parents and children.

4. In domestic swine there is a dominant gene that produces a white belt around the body, while the recessive allele results in a uniformly colored body. One farmer wants only belted hogs, and

another wants only those with a solid color. Which would have the easier task of establishing a pure-breeding stock? Tell how each would accomplish his objective.

5. A cross between two pink-flowered four-o'clocks yields seed that grows into plants with the following flower colors: 24 red, 53 pink, and 28 white. Explain these results by means of a genetic diagram with appropriate letter symbols.

6. A rare dominant human gene results in ptosis (drooping eyelids), characterized by the inability to open the eyelids normally. A man with ptosis marries a woman with normal eyelids. Show the most likely genotype of the parents and the genotypes and phenotypes of their offspring.

7. We can now recognize carriers of many harmful recessive genes such as those for sickle-cell anemia, Tay-Sachs disease, and so on. What practical value can such tests have?

8. Which of the following human traits would probably be the result of a defective functional gene and which of a structural gene: aniridia, absence of the iris of the eyes; albinism, absence of the enzyme to produce melanin; elliptical red blood cells instead of the normal disk-shaped cells? Explain why in each case.

9. People who cannot break down the amino acid cystine have cystinosis, characterized by a high level of cystine in the urine. From what you have learned in this chapter would you expect the gene for this trait to be dominant, recessive, intermediate, or codominant? Explain.

10. A cattleman has a roan bull and white cows but wants a pure-breeding herd of red cattle. How would you advise him to proceed in order to get his red cattle in the least number of generations? Be specific.

6. THE DIHYBRID CROSS

After Mendel discovered the principle of assortment, that gene pairs segregate during the formation of reproductive cells, he began to wonder about the distribution of genes in the hybrids of parents that differed with respect to two or more characteristics. Would the genes from one parent stay together in succeeding generations or would they be independently assorted so that mixtures of maternal and paternal traits would appear? To settle this question Mendel made dihybrid crosses, crosses in which the parents differed with respect to two traits.

INDEPENDENT ASSORTMENT

One of Mendel's first dihybrid crosses involved the shape and color of the seeds in garden peas. After the seeds were dried, some remained round while others became wrinkled. Also some were yellow and some were green. He crossed pure-breeding (homozygous) yellow round with homozygous green wrinkled. The seeds of the F_1 were all yellow round, which indicated that the gene for yellow and the gene for round were dominant. When these F_1s were selfed (allowed to self-pollinate), the seeds of the F_2 proved to be 315 yellow round, 101 yellow wrinkled, 108 green round, and 32 green wrinkled. This was an approximate 9:3:3:1 ratio. From these results Mendel concluded that there had indeed been independent assortment when the gametes of the F_1 were formed. Nothing was holding together the genes from one parent. Later geneticists were to find that there is an exception to this rule. When genes for two different traits are on the same chromosome they are held together to a certain degree during meiosis. This is known as gene linkage and is considered in chapter 13. Perhaps it was
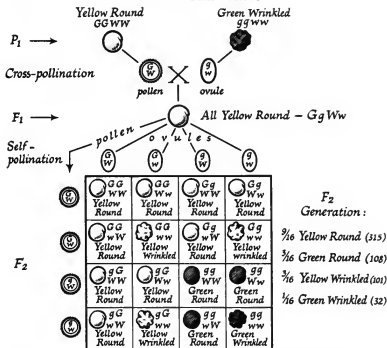
Fig. 6–1. Method of diagramming a dihybrid cross of garden peas as first worked out by Mendel. (From Winchester, Genetics, 2d ed., Houghton Mifflin.)

good that Mendel did not run into any cases of linkage in his dihybrid crosses. If he had he might have become confused and not proposed the principle of independent assortment.

DETERMINING DIHYBRID RATIOS

Determining dihybrid ratios is somewhat more difficult than determining monohybrid ratios, and a number of methods can be used.

The Punnett Square (Checkerboard Method). The Punnett square described in chapter 5 as a means of determining monohybrid ratios can also be used for dihybrid crosses. The F₁ is easy when both parents are homozygous for both genes, since all the offspring will be heterozygous. With free gene recombination, however, four kinds of gametes are produced by the F₁. Thus an *inter*

se cross will require a checkerboard with four squares in each direction, a total of 16 squares. Figure 6–1 shows how such a diagram is prepared.

Some crosses involving two traits do not require the full checkerboard. In a testcross of the F_1 to the double recessive only a single line of four squares is needed. If one parent has only two kinds of gametes and the other four, then only two tiers of the checkerboard are needed.

The Punnett square can also be used for trihybrid crosses and those involving differences in greater numbers of characteristics, although it becomes somewhat cumbersome. An F_1 of a trihybrid, for instance, will produce eight kinds of gametes. Thus the checkerboard will have eight squares in each direction, a total of 64, and the phenotypic ratio will be 27:9:9:9:3:3:3:1. A tetrahybrid would require 16 squares each way and a total of 256 squares in the checkerboard. Table 6–1 shows how rapidly the numbers increase as the number of traits goes up. It illustrates how great the diversity of organisms can be when all of the many allelic genes are considered. Even with so small a number of genes as 20 pairs, the chance of two offspring receiving the same combination is so improbable as to be virtually impossible.

TABLE 6–1
THE KINDS OF GAMETES AND POSSIBLE ZYGOTIC COMBINATIONS FROM DIFFERENT NUMBERS OF PAIRS OF HETEROZYGOUS GENES

Pairs of Genes	Types of Gametes	Possible Zygotic Combinations
1	2	4
2	4	16
3	8	64
4	16	256
5	32	1,024
6	64	4,096
7	128	16,384
8	256	65,536
9	512	262,144
10	1,024	1,048,576
15	32,768	1,073,741,824
20	1,048,576	1,099,511,627,776

The Product of Independent Events. One of the principles of probability states that the chance of two independent (mutually exclusive) events occurring together is equal to the product of the chances of either happening alone. This principle can be used to determine expected dihybrid phenotypic ratios. A dihybrid is simply two monohybrids being considered at the same time. Suppose in analyzing the results of crossing peas we find in terms of color alone 416 yellow and 140 green and in terms of the shape of the seeds only 423 round and 133 wrinkled. Both of these findings fit the 3:1 ratio of monohybrids. Hence we can obtain the chance of any combination of color and shape by multiplication of the monohybrid expectations:

$\frac{3}{4}$ yellow $\times$ $\frac{3}{4}$ round $= \frac{9}{16}$ yellow round
$\frac{3}{4}$ yellow $\times$ $\frac{1}{4}$ wrinkled $= \frac{3}{16}$ yellow wrinkled
$\frac{1}{4}$ green $\times$ $\frac{3}{4}$ round $= \frac{3}{16}$ green round
$\frac{1}{4}$ green $\times$ $\frac{1}{4}$ wrinkled $= \frac{1}{16}$ green wrinkled

This is a quick way of determining any phenotypic combination, and it can easily be extended to trihybrids and higher hybrid numbers. For instance, supposed we wished to include the color of the flowers. We can obtain the chance of a green round purple by additional multiplication:

$\frac{3}{16}$ green round $\times$ $\frac{3}{4}$ purple $= \frac{9}{64}$ green round purple

Phenotypes from intermediate genes and codominant genes are no problem by this method.

The Forked-Line Method. It is often convenient to make the combinations and multiplications by a series of forked lines. First, put down the monohybrid ratio of one trait and connect this with forked lines to the monohybrid ratio of the other trait. For the yellow round crossed to green wrinkled the method would be as follows:

$\frac{3}{4}$ yellow $\Big\langle$
    $\frac{3}{4}$ round $= \frac{9}{16}$ yellow round
    $\frac{1}{4}$ wrinkled $= \frac{3}{16}$ yellow wrinkled

$\frac{1}{4}$ green $\Big\langle$
    $\frac{3}{4}$ round $= \frac{3}{16}$ green round
    $\frac{1}{4}$ wrinkled $= \frac{1}{16}$ green wrinkled

For a trihybrid we would need to add only two more forked lines after each of these resulting combinations.

Simplified Dihybrid Representations. When the number of gametic types in a dihybrid cross is less than four, it is often possible to use a simplified representation like that commonly used for monohybrids. For example, consider the following testcross. In guinea pigs the gene for black hair is dominant over the gene for white hair, and the gene for short hair is dominant over the gene for long hair. On the basis of frequency of the traits we use the letter W for black hair and w for the recessive allele for white hair; the letter L is used for short hair and l for long hair. If an F_1 hybrid is backcrossed to the double recessive parent the results can be predicted as

$$WwLl \times wwll = WwLl + Wwll + wwLl + wwll$$

This genotype can be translated into the 1:1:1:1 phenotypic ratio typical of the dihybrid testcross.

MODIFIED DIHYBRID RATIOS

The dihybrid ratio may be modified by variations in the effects of different kinds of genes.

Intermediate Genes. When one or both of the gene pairs in dihybrid crosses have intermediate inheritance, the ratio will vary from the 9:3:3:1 obtained when both pairs of genes show dominant-recessive relationships. We have learned that the genes for red and white in cattle give a roan coloration in the heterozygote. The polled (hornless) condition is due to a dominant gene, while horns result from a pair of recessive genes. A cross between homozygous polled red and horned white cattle gives offspring that are polled roan. An *inter se* cross of these gives an F_2 with a ratio of 6:3:3:2:1:1.

When both genes are intermediate, the ratio includes even more classes; it is 4:2:2:2:2:1:1:1:1. Such a ratio is found in the snapdragon when a dihybrid cross involving flower color and leaf width is made. When a red-flowered, broad-leaved plant is crossed with a white-flowered, narrow-leaved plant, the offspring are all pink-flowered and have leaves of intermediate width. It is in the F_2 that segregation gives the great variety of combinations in the 4:2:2:2:2:1:1:1:1 ratio.

Epistasis (Masking Genes). The expression of some genes precludes, or blocks, the expression of other nonallelic genes. This

principle is known as epistasis. The genes involved may be either recessive or dominant.

RECESSIVE EPISTASIS. As an example of recessive genes that mask the effect of other genes, let us consider coat color in the mouse. The wild-type mouse has a color known as agouti, an unusual type of gray due to a banded coloring of the hair shaft. A recessive allele *b* of the gene *B* for agouti, when homozygous, causes the coat to be black. Therefore, when you cross a homozygous agouti with a black mouse, you expect all the offspring to be agouti. Some such crosses, however, will yield some white mice. In these cases the parents are heterozygous for the recessive gene for albinism (*Aa*), and about one-fourth of their offspring will receive both recessive genes (*aa*). These mice are white because they cannot produce an enzyme required for pigment production no matter what genes for different colors may be present. Hence the gene for albinism is epistatic to the gene for black or agouti. This is recessive epistasis.

The gene for albinism is present in the human gene pool. A person homozygous for this gene will have no melanin in the skin even if his or her parents have heavy pigmentation. If an albino with dark-skinned parents marries someone with a very fair skin descended from fair-skinned ancestors, the children from such a
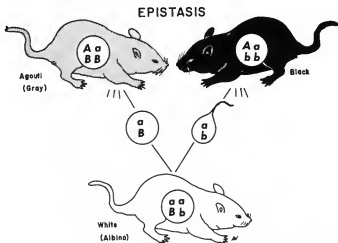

Fig. 6–2. The principle of epistasis illustrated by a cross which yields a white mouse from parents that are gray and black.

union will have rather heavy skin pigmentation because of genes for such pigmentation carried by the albino parent.

Another example of a recessive epistatic gene in humans is the gene *m*, which, when homozygous, causes a person to be a midget, one well proportioned, but much smaller than average size. A person may inherit genes for extreme tallness, yet if he also receives two of these recessive genes he will be a midget. If such a midget marries a person who is homozygous for the normal allele *M* but well under average height because of genes for small stature, the children of such a couple can easily be above average in height.

DOMINANT EPISTASIS. Some dominant genes have an epistatic effect on nonallelic genes. When white Plymouth Rock chickens and white leghorn chickens are crossed, the offspring are all white, as would be expected. An *inter se* cross of these, however, gives an F_2 with a ratio of 13 white to 3 colored. The explanation for this lies in the genotypes of the two breeds of chickens. White leghorns are homozygous for the dominant gene for color *C* but are also homozygous for a dominant gene *I*, which inhibits color formation. Plymouth Rocks are white because they are homozygous for the recessive gene *c* and thus have no gene for color. They are also homozygous for the recessive gene *i*, which means color formation would not be inhibited if the gene for color were present. The cross between the two kinds of chickens would be

$$CCII \times ccii = CcIi$$
(all white because of dominant inhibitor gene)

In the F_2 three of the 16 gene combinations would have at least one dominant gene for color without the dominant gene for inhibition of color. They would be *C–ii* and would be colored. (C indicates CC or Cc.)

The dominant gene for **chondrodystrophic dwarfism** in man causes the arms and legs to be considerably shorter than average, and anyone with this gene is dwarfed in stature even though he may carry genes that would otherwise make him quite tall. This gene is thus epistatic to all the genes for tall stature.

DUPLICATE RECESSIVE EPISTASIS. Hearing is a complex process that requires the coordination of a number of anatomical structures, the development and operation of which are determined by different genes. One recessive gene prevents the normal construction of the auditory nerve, and the homozygous person would

be deaf even though the rest of the hearing apparatus was normal. Another person might have the gene for normal nerves but would inherit a pair of recessive genes that produce a defective receiving apparatus. If these two deaf people married, all their children would have normal hearing because each child would get a dominant gene for normal hearing from each parent. In another marriage between two deaf people all the children would be deaf because the parents were deaf as a result of the same genetic cause. If we use *a* and *b* as symbols for the two recessive genes, the two types of marriage could be represented as follows:

$$aaBB \times AAbb = AaBb \text{ (normal hearing)}$$
$$aaBB \times aaBB = aaBB \text{ (deaf)}$$

This is known as duplicate recessive epistasis because either of two recessive genes, when homozygous, can prevent the expression of the other dominant gene. Figure 6–3 shows the ratio of children that would be expected when two persons heterozygous for both genes marry. The ratio comes out 9 normal hearing:7 deaf.

DUPLICATE DOMINANT EPISTASIS. In this type of epistasis one of either of two dominant genes inhibits homozygous recessives at another locus. Most domestic fowls have unfeathered shanks. They are homozygous for genes we shall designate as *x* and *y*. The presence of either dominant *X* or dominant *Y*, however, will cause the shanks to be feathered. A cross between two chickens that are heterozygous for the two genes yields offspring in a ratio of 15 feathered shanks:1 unfeathered shank. All four recessive genes must be inherited to produce unfeathered shanks.

Modifying Genes. Sometimes one gene is not completely epistatic to another gene but does modify the expression of the latter. A dominant gene *B* that is present in a number of Norwegian families causes a shortening of the index finger (**minor brachydactyly**). The degree of shortening varies considerably, however. It has been found that a second gene accounts for this difference. The recessive gene *m*, when homozygous, somehow modifies the effect, and the finger is only slightly shortened. When the dominant allele *M* is present along with the *B* gene, however, the finger is very short. Hence one gene influences the degree of expression of the other. This condition is known as **variable expressivity** and is considered in greater detail in chapter 18.

EPISTASIS IN DEAF-MUTISM

A & B necessary for normal hearing

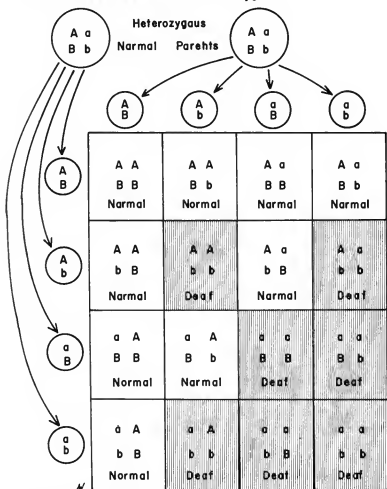a or b deaf-mutism when homozygous

Fig. 6–3. Duplicate recessive epistasis results in the unusual ratio of 9 normal hearing:7 deaf when both parents are heterozygous for two recessive genes for deafness.

Multiple modifying genes may sometimes cause a considerable variation in the degree of expressivity of a gene. A good example of this is human eye color, that old standby used so frequently as

an illustration of human inheritance. We have learned that blue eyes are inherited as a recessive trait while brown eyes are dominant. Common observation, however, shows that there are more eye shades just than these two. We see green eyes, hazel eyes, light brown eyes, and dark brown eyes. The explanation is this: One gene seems to prevent the production of melanin in the iris and the eyes are a clear blue for the same reason that the sky is blue or deep water is blue—the longer wavelengths of light are absorbed. This is a recessive gene for unpigmented iris. The dominant allele codes the production of melanin in the outer part of the iris, but modifying genes determine how much melanin there will be. Some such modifiers cause a very light layer of melanin to be deposited and some of the blue shows through to give green. Genes that cause a heavier deposit of melanin give hazel or light brown eyes and so on, until some have such heavy deposits that the eyes appear black (actually a very dark brown).

This information can help a teacher explain some embarrassing questions that students may bring up. After blue eyes have been studied as an example of a recessive trait, a student may say, "But I have brown eyes and both of my parents have blue eyes. How do you explain that?" Some teachers fall back on the very unlikely event of mutation to avoid implying some extramarital activity on the part of the mother, but modifying genes give a more satisfactory explanation. One parent may carry genes for pigmented eyes but have modifying genes for very light melanin deposits. The eyes, therefore, might be called blue, although they would have a greenish tinge. The other parent could be homozygous for unpigmented eyes and have the pure blue but would carry genes for heavy melanin deposits. The child receiving the dominant gene for pigmentation from the parent with greenish blue eyes and genes for heavy deposits of melanin from the true blue-eyed parent would have decidedly brown eyes.

PROBLEMS

1. In dogs the tendency to bark while trailing game is the result of a dominant gene, while silent trailing is the recessive trait. Erect ears are due to a dominant gene and drooping ears to the recessive allele. Show the expected ratio in the offspring of two erect-eared barkers who are heterozygous for both genes.

2. In minks either gene *p* or *i*, when homozygous, causes a platinum coat color. At least one dominant allele of each of these genes is necessary to produce the common brown color. Show the expected ratio of the offspring of a cross between two brown minks, both of which are heterozygous for both of these genes.

3. A dominant human gene, *B*, causes blaze, a white forelock of the hair. The recessive gene for albinism, *a*, prevents the formation of melanin in any part of the body so the hair is white all over. A man with blaze had an albino mother. He marries an albino woman who had no blaze in either parent. Show the genotypic and phenotypic ratio of children they may have. (*Note:* Since *B* is a relatively rare gene, there is almost no chance that he will have two of them.)

4. Two pairs of genes affect the comb in the domestic fowl. Chickens homozygous for both recessives have a single comb. A dominant allele of one of these genes, *P*, causes a pea comb. The dominant allele of the other, *R*, causes a rose comb. Chickens with at least one of both of these dominants have a walnut comb, looking somewhat like the shell of an English walnut. Show the expected offspring of a cross between two walnut-combed chickens, both of which are heterozygous for both recessive genes.

5. The chestnut color of horses is due to a recessive gene, while the dominant allele causes the coat to be black. The pacing gait is due to a recessive gene, whereas the dominant allele results in the trotting gait. Show the offspring that could result from a cross of a black trotter heterozygous for both genes with a chestnut pacer.

6. A woman with normal hearing has parents who are both deaf. She marries a deaf man, both of whose parents are also deaf. Using the most likely genotypes, predict the expected ratio of deafness to normal hearing in the offspring of this couple. Assume that only the two recessive genes mentioned in this chapter could be responsible for deafness, and remember that these are not common genes. Hence any gene involved is most likely to be the dominant for normal hearing unless you have reason to think otherwise.

7. A person with green eyes marries someone with black eyes (actually very dark brown). They have one child with blue eyes and one with light brown eyes. Assume that only two modifying genes are involved and show the genotypes of both parents and children.

7. PROBABILITY IN HEREDITY

Chance plays an important role in determining which genes shall be transmitted from parents to their offspring. The particular combination of genes that determine your potentialities results from the chance assortment of genes within the gametes that united to start your life. The laws of probability, therefore, come into play when we try to predict the occurrence of any particular combination of genes. Genetic counselors use these laws when advising a couple of the chance that any of their children will express a particular defect. In this chapter we shall consider some of the principles of probability and show how they can be used in making such predictions.

COMBINING PROBABILITIES

Chapters 5 and 6 showed how to determine the proportions of offspring expected from parents of specific genotypes. For instance, in a cross between two heterozygous black guinea pigs we found that the chance for the dominant black is ¾ and the chance for the recessive white is ¼. Let p represent the chance for black and q the chance for white. (We could use a and b or any other letters, but p and q are most commonly used by statisticians.) In a cross between a homozygous black and a white we would find that $p = 1$ and $q = 0$. In a heterozygous black crossed with white, $p = \frac{1}{2}$ and $q = \frac{1}{2}$. In such cases where there are only two kinds of offspring we know that $p + q = 1$ and $q = 1 - p$.

Coincident Happenings. Frequently we want to know the chance that two or more independent events will happen together. This can be determined by application of a simple rule: *The chance of the occurrence of a number of independent events is equal to*

the product of their separate probabilities. Two events are said to be independent if the occurrence of one does not influence the occurrence of the other. For example, if you are tossing two coins and obtain a head on the first toss, it will in no way influence the chance for a head on the toss of the second coin. Hence we can find the chance of obtaining two heads by multiplying the chance for a head on each of the two tosses. Since the chance of a head, p, is $\frac{1}{2}$, then the chance for two heads is p^2, or $\frac{1}{4}$. If we want to know the chance of two black guinea pigs appearing in the offspring of heterozygous parents, we know that $p = \frac{3}{4}$ and $\frac{3}{4}^2 = \frac{9}{16}$. The chance of two whites would be $\frac{1}{4}^2 = \frac{1}{16}$.

We can thus determine the probability of two different traits occurring together. A heterozygous brown-eyed couple want to know the chance that their first child will be a blue-eyed girl. Multiply the chance for blue eyes ($\frac{1}{4}$) by the chance for a girl ($\frac{1}{2}$):

$$p = \text{blue eyes} = \frac{1}{4} \qquad q = \text{girl} = \frac{1}{2} \qquad p \times q = \frac{1}{8}$$
$$\text{(blue-eyed girl)}$$

If the couple are also heterozygous for attached earlobes, we can introduce a third letter, $r = \frac{1}{4}$, and continue multiplication to find the chance that this girl will also have attached earlobes.

$$p \times q \times r = \frac{1}{32} \text{ (blue-eyed girl with attached earlobes)}$$

Using Percentages. In some cases it is more convenient to convert the numerical fractions to percentages. The probability of obtaining two heads when tossing two coins would be $0.50^2 = 0.25$, or 25%. In some cases the percentage method is almost mandatory to avoid using very awkward numerical fractions. For instance, suppose 13.4% of a population in Africa carry the gene for sickle-cell anemia. What is the chance of a marriage between two carriers? It would be $0.134^2 = 0.018$, or 1.8%. The numerical fraction of the population who are carriers would be about 100/746, and when we square this we get about 10/556. It is obvious that in such cases stating the probability as a percentage is less awkward than as a numerical fraction.

The principle can be extended to greater numbers of events by continuing the multiplication. For instance, to get the percentages of cases of sickle-cell anemia in the above population we would have to multiply the chance of marriage of heterozygous parents

by 25%, since only one-fourth of their children will become homozygous for the gene for sickle-cell anemia. We would get 0.018 × 0.25 = 0.0045, or 0.45%, as the frequency of this disease in this particular population. Since those who have the disease usually do not live to reproduce, they do not contribute to the number of children born with the disease. To obtain the chance that heterozygous parents will have four children with the anemia we could continue with multiplication. Such an event would be unlikely, but it could happen in a small proportion of the cases. It would be

$$p = \frac{1}{4} \quad \text{so} \quad p^4 = \frac{1}{256}$$

Therefore, if you found many marriages between heterozygous parents who have four children each, about one out of 256 families would have all four children with the anemia.

Population geneticists often use this principle to calculate the chance of the appearance of a particular trait in the population. We know, for instance, that about one person in 20 in America is a carrier of the recessive gene for cystic fibrosis. This means that about one marriage in 400 is between two carriers, and since ¼ of the children of such marriages will have the disease, about one child in 1600 will have cystic fibrosis. Since the homozygotes who have cystic fibrosis have not lived until adulthood in the past, we do not need to consider them in this calculation. The way to include these homozygous recessives statistically when they do survive is discussed in chapter 17.

Effect of Previous Events. In discussing probability we must also keep in mind the fact that events which have already happened do not influence events yet to come. For instance, suppose a couple who have just married plan to have three children and want to know the chance that all three will be boys. Assuming an equal chance for each sex, the probability of three boys would be ½³, or ⅛. But suppose another couple have already had one boy and want to know the chance for three boys. The odds would be ½² because the chance of a boy on the first birth has now become 1 in 1, not ½. If a couple have already had three boys, they may feel that their chance of having a girl at the fourth pregnancy is greater than it would be if they had had no children. The chance for a girl is still ½, however, because the previous pregnancies are truly independent events that do not influence future happen-

ings. The kind of sperm that fertilizes the egg determines sex, and male- and female-determiners are produced in approximately equal proportions. The male-determining sperm do not know that the couple already have three boys and that they should hold back and give the female-determining sperm their turn. Each type of sperm is just as likely to be successful as if the couple had had no previous children.

In applying this principle of probability one must be sure that the events are truly independent of one another. For instance, suppose $\frac{1}{3}$ of a population in Minnesota have blue eyes. About $\frac{1}{4}$ of the total population have naturally blond hair. Hence one might conclude that the chance of any one person having blue eyes and blonde hair is $\frac{1}{12}$, but this assumption would be erroneous. Blue eyes and blond hair are not mutually exclusive traits. They are more likely to be found in the same person than chance assortment would indicate. Many people in this region have ancestors from the Scandinavian countries, many of whom had blue eyes and blond hair. Hence the two traits have a great likelihood of appearing together in their descendants.

Reverse Application of Principle. When we know the chance of two events of equal probability happening together, we can determine the chance of either happening separately by reversing the method and taking the square root of the chance of the occurrence of both events. This method is often used to determine the frequency of a recessive gene in a population. We can learn what portion of a population has two of these recessive genes by simply tabulating the number of persons who show the trait. For instance, we can go to hospital records and find that about one child in 1600 born there had cystic fibrosis. To determine the frequency of one gene for cystic fibrosis existing in a normal carrier, we take the square root of $\frac{1}{1600}$ and get $\frac{1}{40}$. This means that one gene in 40 at this particular locus on a chromosome is for cystic fibrosis. Since each person has two of these chromosomes, however, we must multiply this figure by 2 and get $\frac{1}{20}$ as the frequency of carriers.

Percentage can also be used. If we find that 49% of a population have type O blood, which is a recessive trait, we can get the frequency of the gene for O at this locus by taking the square root of 0.49 and get 0.70, or 70%. This leaves only 30% of the genes at this locus for the genes for A and B antigens.

Keep in mind the fact that the two events must be of equal

probabilities. The chance of heterozygous parents having an albino girl is $\frac{1}{8}$, but we cannot find the chance of an albino of either sex by taking the square root of $\frac{1}{8}$. The chance for a girl and the chance for an albino are different.

Chance of Either of Two Events Happening. The probability of either of two or more independent events is equal to the sum of their individual probabilities. It is obvious that the chance for a couple to have either a boy or a girl would be $p + q = 1$, if we leave out the very rare cases of a third choice, a hermaphrodite of mixed sex. If a couple are heterozygous for both sickle-cell anemia and for cystic fibrosis, then the chance that they will have a defective child (one with either or both of these two afflictions) would be $\frac{1}{4} + \frac{1}{4} = \frac{1}{2}$. We know that the frequency of the gene for cystic fibrosis in the gene pool of the United States is about one in 40, so the chance of a person carrying the gene is $\frac{1}{20}$. We get the $\frac{1}{20}$ by adding the chance that the gene will be on one chromosome of a pair of this kind of chromosome to the chance that it will be on the other chromosome of the pair. Hence $\frac{1}{40} + \frac{1}{40} = \frac{1}{20}$.

More than two events can also be considered. We know the chance of drawing a king from a deck of cards is $\frac{1}{13}$, since there are four kings in a deck of 52 cards. The other face cards exist in the same proportions. Then what is the chance of drawing any face card (jack, queen, or king)? It would be $\frac{1}{13} + \frac{1}{13} + \frac{1}{13} = \frac{3}{13}$.

Chance of Mixed Probabilities (Permutations). Sometimes we would like to know the chance of obtaining certain mixtures of independent events. A couple may plan on having children and would like to have two of each sex. If they wish to know the chance that the first two will be boys and the second two girls, the principle of multiplying the probabilities of independent events can be employed: $p \times p \times q \times q = \frac{1}{16}$. Such specification of the sequence of events is known as a permutation.

Chance of Mixed Probabilities (Combinations). It is not likely that a couple planning to have four children would care about the sequence; they would probably want to know only the chance that they will have two of each sex. This type of determination is known as a **combination** and requires a more complex method to solve. Several methods can be used to get the prob-

abilities of combinations. We can apply the principle of either/or events and add the chance of each of the possible permutations. Hence to get the chance of two boys and two girls in any sequence we would add all possible permutations.

boy-boy-girl-girl = $\frac{1}{16}$
boy-boy-girl-girl = $\frac{1}{16}$
boy-girl-girl-boy = $\frac{1}{16}$
girl-girl-boy-boy = $\frac{1}{16}$
girl-boy-girl-boy = $\frac{1}{16}$
girl-boy-boy-girl = $\frac{1}{16}$

Total $\frac{6}{16}$, which is the chance of two boys and two girls in any sequence.

This method can become somewhat awkward, so one can employ an algebraic equation.

Allow P = probability
n = total number of events (births) = 4
s = number of one event desired (boys) = 2
t = number of other event desired (girls) = 2
p = chance of one event (boy) = $\frac{1}{2}$
q = chance of other event (girl) = $\frac{1}{2}$

The equation is

$$P = \frac{n'}{s' \; t'} \; p^s \; q^t$$

In this equation we use the sign n' or n factorial. In employing a factorial you state the value of n and multiply by all lower numbers down to 1. In this problem $n = 4$, so $4' = 4 \times 3 \times 2 \times 1 = 24$. The same applies to s' and t'. The entire problem and its solution would then be

$$\frac{4 \times 3 \times 2 \times 1}{2 \times 1 \times 2 \times 1} \times \frac{1}{2}^2 \times \frac{1}{2}^2 = \frac{6}{16}$$

This method can be applied to problems where there are more than two probabilities. For instance, a cross between two roan cattle have an expected ratio of 1 red:2 roan:1 white in their offspring. If you obtain four calves from such crosses, what is the chance that they will come out in this exact ratio?

$n = 4 \quad s = 1 \quad t = 2 \quad u = 1 \quad p = \frac{1}{4} \quad q = \frac{1}{2} \quad r = \frac{1}{4}$

$$P = \frac{n'}{s'\ t'\ u'}\ p^s\ q^t\ r^u$$

$$P = \frac{4'}{1'\ 2'\ 1'}\ \frac{1}{4}\ (\frac{1}{2})^2\ \frac{1}{4}\ =\ \frac{3}{16}$$

Thus we find that even though 1:2:1 is the expected ratio mathematically, if there are only four offspring, the chance of obtaining that exact combination is rather small.

The method can be extended to even greater numbers of probabilities, although you may have to use a computer to calculate the answers. For instance, in the second generation of a cross between homozygous black short and white long guinea pigs, what is the chance that you will get exactly a 9:3:3:1 ratio in 16 offspring? The problem can be set up as

$$P = \frac{16'}{9'\ 3'\ 3'\ 1'}\ (\tfrac{9}{16})^9\ (\tfrac{3}{16})^3\ (\tfrac{3}{16})^3\ (\tfrac{1}{16})$$

It would be hard to perform these calculations by computer because the figures would run up in the trillions.

A third method can be used that involves the expansion of the binomial $(p + q)^n$. To solve the problem of the chance of obtaining two boys and two girls in a family of four we would use

$$(p + q)^4 = p^4 + 4p^3q + 6p^2q^2 + 4pq^3 + q^4$$

Since the exponents indicate the number of events desired, we would choose the middle one for two boys and two girls. If p represents a boy with a chance of $\frac{1}{2}$ and q represents a girl with a chance of $\frac{1}{2}$, the answer would be:

$$6p^2q^2 = 6(\tfrac{1}{2})^2 \times (\tfrac{1}{2})^2 = \tfrac{6}{16}$$

It is easy then to get the chances for any one or all combinations by multiplying out each term of the binomial:

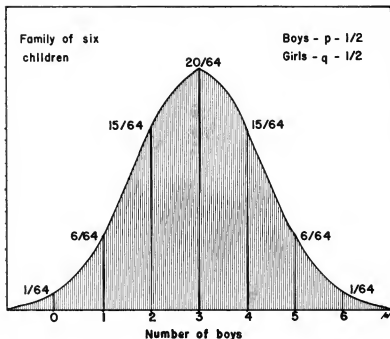|	
4 boys-no girls	1 boy-3 girls
$\frac{1}{16}$	$\frac{4}{16}$
3 boys-1 girl	4 girls
$\frac{4}{16}$	$\frac{1}{16}$
2 boys-2 girls	
$\frac{6}{16}$	

Fig. 7–1. In families with six children the distribution of boys and girls is plotted in the form of a bell-shaped curve.

Note that this distribution forms a bell-shaped curve when plotted on a graph, which will be true in all cases where the chances for two events are equal. If the chances are not equal, we obtain a skewed curve as shown in figure 7–2.

The expansion of the binomial to five events is given below to illustrate additional combinations. Remember that the exponents after the letters indicate the number of each event.

$$(p + q)^2 \qquad p^2 + 2pq + q^2$$
$$(p + q)^3 \qquad p^3 + 3p^2q + 3pq^2 + p^3$$
$$(p + q)^4 \qquad p^4 + 4p^3q + 6p^2q^2 + 4pq^3 + q^4$$
$$(p + q)^5 \qquad p^5 + 5p^4q + 10p^3q^2 + 10p^2q^3 + 5pq^4 + q^5$$

If you want to find the chance that heterozygous parents will have two children with normal pigmentation and one with albinism you would choose $3p^2q$ from the line of $(p + q)^3$. The answer would be $27/256$.
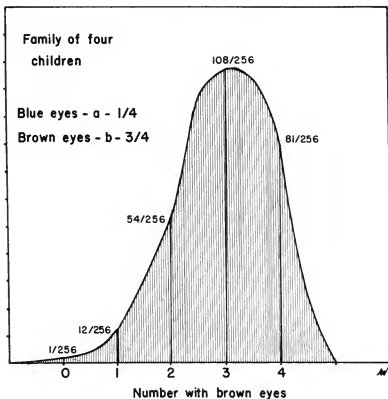
Fig. 7–2. A skewed curve results when the chance of two events of unequal probabilities are considered.

STATISTICAL ANALYSIS OF RESULTS: CHI-SQUARE

The results actually obtained from genetic crosses seldom coincide exactly with the mathematical calculation. In a cross between a heterozygous black and a white guinea pig we would not think it unusual if we got 6 black and 2 white, even though we have the mathematical expectation of 1:1 or 4 black and 4 white. The birth of each guinea pig represents a chance event with respect to color, and chance can cause such deviations from the ratio. In fact, it is even possible to get all white in eight births. Such an event would occur in about one out of 256 such crosses. As the number of offspring becomes larger, however, they more closely reflect the

expected ratio. If we obtained 100 offspring from a number of guinea pig crosses of the type described above, we would tend to get results that would cluster around the 1:1 ratio. We might get 56 black and 44 white, but this is obviously a chance variation from the ratio. When the deviations become greater, however, we might begin to have doubts. If we got 63 black and 37 white, we might think that something other than chance was operating. Perhaps the homozygous white guinea pigs do not survive intrauterine existence as well as the blacks so their number at birth is reduced. Where do we draw the line, however, between differences that are obviously chance variations and those that result from the operation of some other factors? We need some statistical measure of **goodness of fit** of our results to the mathematical expectation. One popular statistical tool is **chi-square**. This can be represented by the following equation:

$$x^2 = \sum \frac{d_o^2}{e}$$

d_o = deviation of the observed (obtained) results from those expected by mathematical calculations

e = expected results according to the mathematical ratio

Σ (capital sigma) = sum of

We can apply this measure to the first set of figures given for the black and white guinea pigs in 100:

| Expected black = 50 | Expected white = 50 |
| Obtained black = 56 | Obtained white = 44 |

$$x^2 = \frac{6^2}{50} + \frac{6^2}{50} = 1.44$$

We now match this chi-square value to table 7–1 to determine the goodness of fit of the results. For this problem we use the top line of figures, which represent one **degree of freedom**. The degree of freedom is always one less than the total number of pertinent classes. We have two possible kinds of guinea pigs so there is one degree of freedom. If a guinea pig is not black it must be white, there is no second choice, hence only one degree of freedom. When there are four possible kinds of offspring, as in a dihybrid cross, there would be three degrees of freedom; there would be a choice through the first three combinations, but if a

TABLE 7–1
CHI-SQUARE VALUES AND CHANCE OCCURRENCE

Degrees of Freedom	Possibility of Chance Occurrence in Percentage (5% or Less Considered Significant)								
	90%	80%	70%	50%	30%	20%	10%	5% (sig.)	1%
1	0.016	0.064	0.148	0.455	1.074	1.642	2.706	3.841	6.635
2	0.211	0.446	0.713	1.386	2.408	3.219	4.605	5.991	9.210
3	0.584	1.005	1.424	2.366	3.665	4.642	6.251	7.815	11.341
4	1.064	1.649	2.195	3.357	4.878	5.989	7.779	9.488	13.277
5	1.610	2.343	3.000	4.351	6.064	7.289	9.236	11.070	15.086
6	2.204	3.070	3.828	5.348	7.231	8.558	10.645	12.592	16.812
7	2.833	3.822	4.671	6.346	8.383	9.803	12.017	14.067	18.475
8	3.490	4.594	5.527	7.344	9.524	11.030	13.362	15.507	20.090
9	4.168	5.380	6.393	8.343	10.656	12.242	14.684	16.919	21.666

guinea pig did not fall into any of the first three categories, it would have to be the fourth.

The chi-square value in this case falls between the 20% and 30% columns. This means that the chance that we would obtain a deviation this great or greater on any one cross would be between these frequencies. With such a high probability this deviation would certainly not be considered significant. When the chi-square falls below the 5% column, we begin to think that something other than chance is influencing the results. Deviations of such magnitude would occur only once in twenty times; another way to put it is that such a deviation has only a 5% chance of being due to chance.

In this problem we can say that P, the probability of such an occurrence by chance, is less than 20% and greater than 30%. A short way of expressing this is $20\% < P < 30\%$. We can be more specific, if need be, by extrapolation. The chi-square at 20% is 1.642 and at 30% it is 1.074; this is a difference of 0.568. The chi-square obtained is 0.366 above the figure for a 20% chance. This lies at about 65% of the difference between the two percentages. Thus $P = 26.5\%$ (65% of 10% added to 20%).

If we apply chi-square to our second example where we got 63 black and 37 white guinea pigs, we would find:

Expected black $= 50$ Expected white $= 50$
Obtained black $= 63$ Obtained white $= 37$
Deviation black $= 13$ Deviation white $= 13$

$$x^2 = \frac{13^2}{50} + \frac{13^2}{50} = 6.76$$

$$P < 1\%$$

Since the chance that we would get this great a deviation at any one cross is slightly under 1%, we can feel rather confident that something other than chance accounts for the difference. The gene that makes the coat white must also reduce viability in the embryo.

Sometimes it may be more convenient to use a tabular method of obtaining chi-square, especially when several classes of events are involved. This is illustrated below with the results obtained by Mendel in his dihybrid cross of garden peas. There are three degrees of freedom in this case.

Phenotype of F_2	Observed x	Expected e	Deviation Squared d^2	$\dfrac{d^2}{e}$
Yellow round	315	313	4	0.0128
Yellow wrinkled	101	104	9	0.0865
Green round	108	104	16	0.1538
Green wrinkled	32	35	9	0.2571
	556			$x^2 = 0.5102$

Upper limits of chi-square at 5% level of significance 7.815

$$P > 90\%$$

Since P is greater than 90%, there is no doubt that the small deviations Mendel obtained were due to chance alone. In fact, his results agree so closely with those expected in his tabulations that some have wondered if he did not alter them a little to make them adhere more closely to the predicted ratios.

Two precautions should be kept in mind when using chi-square. First, it cannot be used with percentages; the actual numbers obtained must be used. Second, the results become less reliable when the number of expected events in any class is small. Generally we feel that the number of events should exceed five.

PROBLEMS

1. A man has the dominant trait of potato nose, an enlargement of the nose that causes it to roughly resemble a potato. What is the chance that any particular great-grandchild of this man will have potato nose?

2. About $\frac{1}{30}$ of the Jewish people from northeastern Europe carry the gene for Tay-Sachs disease. In a certain borough of New York City about ¼ of the people are Jews with an ancestry from this region. If any person is chosen at random, what are the chances that he will carry this gene?

3. A couple find that they both have type B blood. What is the chance that their first child will have type O blood? (About $\frac{3}{7}$ of those with type B blood carry the recessive gene for type O.)

4. The tendency to develop hemolytic jaundice results from a dominant gene, but only 10% of those with this tendency develop the disease. A man develops the disease, but his wife is homozygous for the recessive normal gene. They have one child. What is the chance that the child will develop the disease?

5. Statistics show that about one child out of each 10,000 born in the United States has PKU (phenylketonuria). What is the frequency of this gene in the normal population and what proportion of the people carry the gene?

6. If one person in 20 is a carrier of the gene for cystic fibrosis, what is the chance that the next two babies born in a certain hospital will both have cystic fibrosis? What is the chance that one of the two will have it?

7. Either of two recessive genes can cause deafness. A couple with normal hearing are both heterozygous for both genes. What proportion of their children would be expected to be deaf? Use a probability method to obtain the answer.

8. A newly married couple plan to have three children and would like to have boys on the first two births and a girl on the third. What are the chances that their wishes will be fulfilled? Another couple also want two boys and a girl, but they do not care in what sequence they appear. What are their chances? Use both the factorial and the $(p + q)^n$ methods to get answers.

9. A couple with normal pigmentation have an albino child. If they have three more children, what are the chances that two will

be albino girls and one a normal boy? Use $(p + q)^n$ on this problem.

10. A black couple in Philadelphia have four children with sickle-cell anemia, four who carry the gene for this condition, and two who are homozygous normal. Use the factorial method to set up the chance that this particular combination will be obtained. Do not work this out unless you have access to a computer, as the numbers will get quite large.

11. Native Hawaiians have about 60% type A blood. A group living on the island of Kauai claim that they are pure Hawaiians and that there has been no gene flow in from other races. A group of 100 of these are typed and 50 are found to be type A while the other 50 are other types. Use chi-square to determine if there appears to have been any gene flow from races with smaller type A percentages or if this is just a chance variation in blood type for this particular group tested.

12. In one of Mendel's test crosses of a dihybrid he obtained 24:26:21:29. Use chi-square to determine if this is a true reflection of the expected ratio.

13. In an isolated group of 228 Pennsylvania Germans known as the Dunkers, Bentley Glass found 137 with type A blood. The general white population of the United States has about 40% type A blood. Do the Dunkers show a significant deviation from this percentage?

8. SEX DETERMINATION

Sex is an almost universal characteristic of living matter. With the exception of the viruses some form of sex has been discovered in all living things. We tend to equate sex with reproduction because the two are always associated in larger animals, but many organisms can reproduce asexually. Sex accomplishes one important thing—it brings about the combination of genes from two different organisms. The new genotypes and the variety of phenotypes that result from this combination are necessary if there is to be any significant degree of natural selection. Many simpler animals and many plants reproduce quite efficiently asexually, but they have some means of exchanging genes to provide variety. Some simpler animals and many plants have both sexes in one body, but even these usually do achieve cross-fertilization. The separation of the sexes that exists in many plants and in all higher animals permits each sex to carry out its role more efficiently. When sexes are separate, however, there must be some way to ensure the production of somewhat equal numbers of males and females.

All organisms seem to be bipotential as to sex, that is, all have the genes that can produce both male and female characteristics. The most masculine man has the genes responsible for the development of a woman, and vice versa. Sex is determined, then, by some event that sets in motion the development of the characteristics of one sex while inhibiting those of the opposite sex. Let us examine some of the triggering mechanisms.

SEX DETERMINATION IN BACTERIA

For many years bacteria were assumed to have no sex. They reproduced asexually by fission, but no kind of sexual union seemed to occur. The single circular chromosome would duplicate and

then the cell would split in half, each daughter cell receiving one of the chromosomes. In 1946 Lederberg and Tatum found that when different strains of bacteria grew together in a liquid medium, some individuals were produced with characteristics of both strains. It was not until the electron microscope was invented that the method by which the bacteria exchanged genes was observed. Two bacteria come in contact and form a conjugation tube through which the genes from one can pass to the other.

Conjugation has been studied particularly in *E. coli*. The chromosome of this bacterium is a circular DNA chain that lacks the protein component characteristic of the chromosomes of higher organisms. In addition some of these bacteria have a small body, the **F factor,** and play the role of gene transmitter during conjugation. When these donor cells, as they are called, come in contact with F⁻ cells (those without the F factor), the F factor
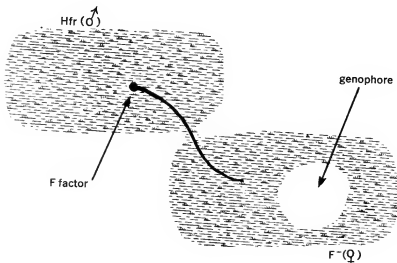

Fig. 8–1. Sex in bacteria. The Hfr, male bacterium, is shown injecting his chromosome into an F⁻, female recipient. Although the cells are not reproducing, it is a sexual union because genes from two different organisms are mixed.

may replicate, whereupon one of the two resulting F factors enters the recipient F⁻ cell. This makes the recipient F⁺.

Sometimes the F factor of an F⁺ cell becomes integrated into the chromosome and the cell becomes an **Hfr** (high frequency recombination). This type of cell can now insert part of its chromosome into an F⁻ cell. During conjugation the circular chromosome of the Hfr cell becomes disjoined at the point of the F attachment. The chromosome then replicates and one end of the newly forming chromosome strand begins entering the recipient. Most of the time the two conjugating bacteria separate after only part of the chromosome has entered, so the recipient becomes diploid for only some of its genes. This diploid state is only temporary, however, because in succeeding fissions some of the recipient's genes may be thrown off and portions of the donor's chromosome may become incorporated into the recipient chromosome. The cells that are formed will thus have new gene combinations, and variety is achieved.

ENVIRONMENTAL SEX DETERMINATION

In a few animals sex is determined by environmental conditions. In the marine worm, *Bonellia*, for example, all newly hatched worms will become females if they are reared apart from others of their species. If a newly hatched larva comes near a mature female, however, it will attach itself to her proboscis where it absorbs a substance that transforms it into a male. The male remains very small and migrates down to the female's genital tract where he lives as a parasite for the rest of his life, his only function being to fertilize the eggs as they are produced. This method does provide for the production of both sexes. The first eggs in any locality will become females; some of the larvae hatching out later will find these females and become males. Certain marine snails and a few other marine invertebrates also have environmental sex determination, but this system is not very efficient, for it tends to produce varying numbers of the two sexes.

SEX DETERMINATION BY CHROMOSOMES

In most forms of life that have separate sexes, variations in their chromosomes trigger the development of one sex or the other. In 1891, when chromosomes were thought to be only a curiosity

related to cell division, H. Henking, a German biologist, saw a peculiar structure in the nucleus during spermatogenesis of certain insects. He noted that half the sperm received this body and half did not. He called this structure the X-body (X for unknown), not even recognizing it as a chromosome. In 1902 C. E. McClung verified this observation in the grasshopper, correctly identified it as a chromosome, and suggested that it was related to sex determination. Soon it became known as the X chromosome. It was found also to exist in many animals and some plants.

The role of chromosomes in determining sex is somewhat different in different species, although several basic methods occur. The XY method is by far the most common.

The XY Method in *Drosophila*. During the early days of *Drosophila* genetic studies it was found that its diploid chromosome number was eight. In the female the chromosomes were seen as four matched pairs, but in the male only three pairs were matched while the fourth pair consisted of one long, rod-shaped chromosome and a J-shaped chromosome. The rod-shaped one was identified as the X chromosome, while the J-shaped one was the Y chromosome. They became known as sex chromosomes because they were found to be related to sex determination. The other chromosomes are the autosomes. During spermatogenesis the X and Y chromosomes pair and later separate so that half the sperm receive the X chromosome and the other half receive the Y chromosome. Each egg has an X. Sex determination depends on which of the two kinds of sperm fertilizes the egg.
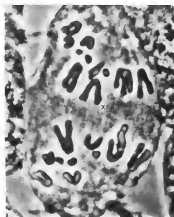

Fig. 8–2. The X chromosome stands out clearly in this primary spermatocyte from a grasshopper. The other chromosomes, autosomes, are all synapsed with homologous mates, but there is only one X, so it stands alone.
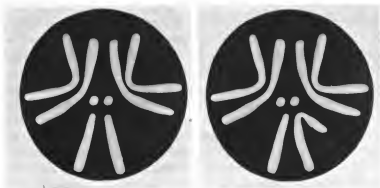
Fig. 8–3. Sex chromosome differences in Drosophila melanogaster represented by models. The female has two of each kind of chromosome, including the rodlike X's, while the male has one X chromosome and one Y chromosome.

These observations led to speculation on the role of the sex chromosomes. One possibility was that the Y chromosome included some sort of male-determining genes. This supposition was dispelled when some females were found to have a Y chromosome in addition to their two X chromosomes. This rare condition occurs when the sex chromosomes fail to disjoin during meiosis and both chromosomes go to one gamete, which is then fertilized by a Y sperm. Other oddities of sex chromosome combinations can also arise as a result of this nondisjunction of the X's:

1. Two-X egg fertilized by X sperm. A **trisomy-X** zygote results, which forms what is sometimes called a **superfemale**, but the fly is of low viability and is sterile.

2. Two-X egg fertilized by Y sperm. The XXY zygote becomes a female, normal in appearance and fully fertile.

3. No-X egg fertilized by an X sperm. The resulting fly is male, normal in appearance but sterile.

4. No-X egg fertilized by a Y sperm. The zygote fails to develop. The X chromosome carries many genes and some of these are vital for development, so no zygote can develop without at least one X.

Nondisjunction of the sex chromosomes can also occur in spermatogenesis, resulting in some sperm having both X and Y

TABLE 8–1
GAMETIC COMBINATIONS AND THE SEX OF THE ZYGOTE IN
Drosophila

Egg	Sperm	Zygote	Ratio male : female	Sex
	AX	AAXX	2:3	female
AX	AY	AAXY	2:1.5	male
	AXY	AAXXY	2:3	female
AXX	AX	AAXXX	2:4.5	superfemale
	AY	AAXXY	2:3	female
AAX	AX	AAAXX	3:3	intersex
	AY	AAAXY	3:1.5	supermale

A—Haploid set of autosomes, male value of 1
X—X chromosome, female value of 1.5
Y—Y chromosome, value of 0

chromosomes, and some sperm lacking either sex chromosome. When these fertilize normal eggs, they will give XXY zygotes and X zygotes.

These results indicate that in *Drosophila* the Y chromosome has nothing to do with sex determination, but it must contain some genes that are necessary for male fertility. The number of X chromosomes seems to determine sex, one X producing a male and two X's producing a female. Further observation bears out these assumptions. On rare occasions there can be nondisjunction of all the chromosomes to give a diploid gamete. When such gametes unite with normal haploid gametes, triploid zygotes result. The following chromosome combinations have been found in triploid zygotes. The letter A represents a haploid set of autosomes.

1. AAAXXX. Female
2. AAAXXY. Intersex, about halfway between male and female

C. B. Bridges proposed the **ratio theory** of sex determination in the light of these observations. He assumed that the autosomes carry genes that tend to trigger the expression of maleness, while
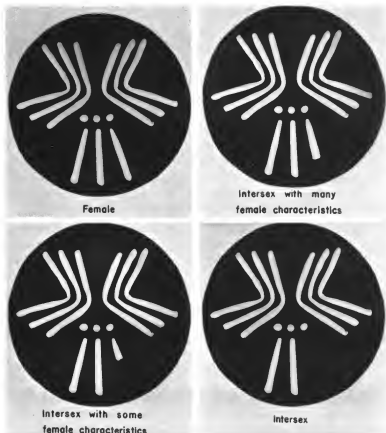
Fig. 8–4. These results with triploid Drosophila melanogaster indicate that genes for female determination are located on the X chromosome. The triploid fly with three X chromosomes is female, in accordance with the ratio theory.

the X chromosome carries genes that tend to trigger femaleness. He assigned a value of 1.5 to the X; a haploid set of autosomes (three chromosomes) was given a value of 1. The various zygotic combinations shown in table 8–1 illustrate this theory. Other observations showed that triploid flies with two X's and a part of a third X showed various degrees of intersexuality depending on how big a piece of a third X was present.

The XY Method in Humans. Human beings are among the

many animals and plants that have the XY method of sex determination, but the results of nondisjunction indicate that the role played by the sex chromosomes is somewhat different from that in *Drosophila*. These differences are apparent in the tabulation below.

1. In humans XXX is a trisomy female, again sometimes called a superfemale, but unlike *Drosophila*, most of these individuals are normal in appearance and many are fertile. Many women are unaware of having this extra X chromosome and discover it only when a routine analysis is made for other purposes. Some have menstrual disturbances, and there is a tendency to mental retardation. About one baby girl in each 1200 is born with trisomy-X, but the frequency of XXX females in mental hospitals is at least twice this number.

2. XXY is a male with **Klinefelter's syndrome.** The male sex organs are only about half normal size and the testes do not produce sperm or adequate amounts of male hormone. The musculature is somewhat feminine and in some there is breast development. Also the stature is somewhat taller than the male average. About one out of each 400 live-born males has this syndrome.

Fig. 8–5. Klinefelter's syndrome. This person is male, but has some breast development and feminized musculature. The testes are only about half normal size. He has the XXY sex chromosome complement. (Courtesy C. Povl Riis.)

3. XO, or single-X zygote, results in a female who does not mature sexually. Girls with this combination are said to have **Turner's syndrome.** They tend to be short and somewhat chunky in body build and have a thick fold of skin on the side of the neck that makes the neck appear very wide when viewed from the front or back. The ovaries consist primarily of connective tissue. Only about one of each 2500 female live births has this syndrome, but a check of the sex chromosomes of spontaneously aborted fetuses shows a frequency that has been reported as high as one in fifty. The XO combination must be highly lethal during fetal development. The frequency of XO and XXY zygotes should be equal if only nondisjunction is involved, but this higher rate of XO's indicates that a lagging of the X chromosome during oogenesis must result in a high number of eggs without an X. The X fails to get included in the nuclear membrane.

4. YO, or single-Y zygote, dies as in *Drosophila*. The X carries genes necessary for life.

These results from abnormal sex chromosome distribution indicate that the human Y chromosome must carry genes that trigger maleness because all those having a Y are male. The ratio of the X's to the autosomes, however, seems to be a factor because a single X zygote (XO) produces an underdeveloped female and a male with two X's is feminized and sterile.

An XYY sex chromosome combination has also been found. This can arise when nondisjunction of the two Y's occurs in the second meiosis to give some sperm that are YY. Karyotype analysis of men imprisoned for violent crimes revealed a high proportion with XYY. These men were somewhat taller than average and somewhat duller mentally. As more karyotypes of men outside of prison were made, however, many were found with XYY who were leading normal lives. Hence there was a question as to whether this chromosome combination created a predisposition to violent criminal behavior. To try to answer this question a screening program for XYY was initiated at the Boston Women's Hospital in 1968. All newborn males were tested and a follow-up study was made to see if the XYY males had a behavior pattern different from that of XY males. Opposition developed, however, because some claimed that a child should not be stigmatized by the knowledge that he was XYY and that he might actually engage in anti-

social behavior because he would think it was expected of him. Also parents might treat such sons differently. As a result the program was terminated in 1975.

The XO Method in Insects. Some insects, such as grasshoppers, crickets, katydids, roaches, and bugs, have X chromosomes but no Y chromosomes. This method of sex determination resembles the XY method, except that the lack of one sex chromosome results in a male. The Y carries very few genes anyway, so its
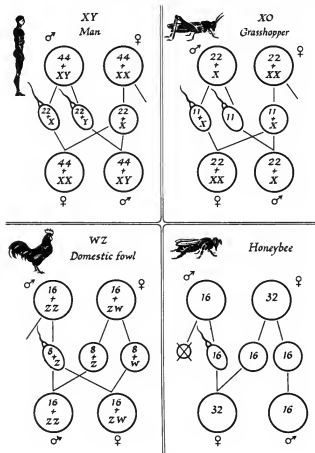

Fig. 8–6. *Variations in the chromosome method of sex determination in different forms of animal life. (From Winchester, Genetics, 2d ed., Houghton Mifflin.)*

absence makes no great difference. In *Drosophila* the XO zygote makes a male, but it is sterile. If the genes on the Y that confer fertility to the male could be transferred to other chromosomes, then *Drosophila* could be said to have XO sex determination.

The ZW Method. In some animals the unlike pair of sex chromosomes is found in females. The females are the **heterogametic** sex while the males are **homogametic.** We usually designate the Z chromosome as the equivalent of the X and the W chromosome as the equivalent of the Y to avoid confusion. Sperm are all Z and eggs may be either Z or W. The trigger for sex determination is reversed from that in the XY method. Butterflies, moths, caddis flies, birds, and some fish have this method.

The Honeybee Method. In honeybees and certain other *Hymenoptera* the males are haploid and the females are diploid. Eggs are produced by normal oogenesis and are haploid. In spermatogenesis, however, there is no pairing of chromosomes so all the chromosomes become included in one sperm cell. Females, such as the queen bee, are inseminated and retain these haploid sperm within a seminal receptacle. The queen can lay either fertile or infertile eggs. By constricting the tube leading from the seminal receptacle, she prevents sperm from reaching the eggs and lays infertile eggs. Such eggs hatch into haploid males, while fertilized eggs become diploid females. In a beehive the great need is for worker females, and the queen allows the majority of the eggs to be fertilized. Some drones (males) are produced so that one will be available when a newly emerged queen is ready for insemination. Since the chromosome ratio is the same for the two sexes and there is no Y chromosome, one might wonder how sex is determined. It has been suggested that there are factors in the cytoplasm for maleness that will be expressed unless there is a diploid set of genes to suppress them.

Sex Chromosomes in Plants. Sex determination is simple in plants with a dominant haploid generation. In *Sphaerocarpus,* a liverwort, there are 14 autosomes, an X chromosome, and a Y chromosome in the small amount of diploid tissue that is formed by the union of sperm and egg. When meiosis occurs to produce the spores, however, about half of the spores will have 7 autosomes and the X, and the other half will have 7 autosomes and the Y. Spores having the X grow into female thalluses while those having the Y grow into male thalluses. In this plant, obviously, the

genes to trigger femaleness are on the X, and those that trigger maleness are on the Y.

Most diploid plants have the XY method, although a few have the XO or the ZW methods. A study by Westergaard and Warmke on *Melandrium*, a seed plant in the pink family, revealed that the male-determining genes are apparently on the Y chromosome. The species studied had 24 chromosomes—12 equal-sized pairs in the female and 11 equal pairs plus the unequal X and Y in the male. Occasional tetraploid plants are found. These fall into three types: those with 44 autosomes and four X chromosomes, which are female; those with 44 autosomes, two X chromosomes, and two Y chromosomes, which are male; those with 44 autosomes, three X chromosomes, and one Y chromosome, which are also male. These results indicate that the Y chromosome carries the male-determiners and that plants lacking a Y are female. The number of X's seems not to be a factor. Triploid plants confirm this assumption. When diploids are crossed with tetraploids, they produce triploids with three of each kind of autosome. Those having one Y or two Y's are male, and those having all three X's are female. The most convincing evidence, however, comes from polyploid plants that contain fragments of the Y chromosome. When only about one-half of a Y is present, the plant is an intersex.

SEXUAL DISTINCTIONS OF INTERPHASE CELLS

When human chromosome studies showed that a number of abnormalities of sex result from sex chromosome irregularities, a need arose for a screening procedure whereby newborns could be checked for such irregularities. With early detection, hormone treatment and possibly surgical operations can help the child grow into a person as nearly normal in sex as possible. Complete karyotyping of each newborn, however, would require considerable time of experienced personnel.

Barr Bodies. Murray Barr, at the University of Western Ontario, found a darkly stained body in the nucleus of cells from female cats, but no corresponding body in cells from male cats. These bodies were later found in many other mammals including human beings. We now call these **Barr bodies**, or **sex-chromatin bodies**.
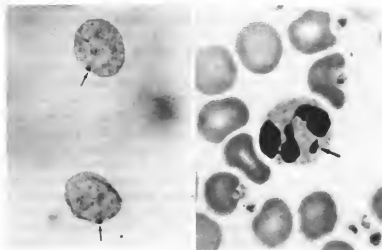
Fig. 8–7. *Barr bodies and drumsticks. The darkly stained bodies lying against the nuclear membrane of the cells on the left are from the mouth of a girl. They are the Barr bodies, or sex chromatin bodies. The drumstick projecting from the nucleus of the white blood cell at right is also found only in female cells.*

Later it was found that a Barr body represents a coiled X chromosome, and there is always one less Barr body than there are X chromosomes in the cell. In a normal female, therefore, one X uncoils while the other remains coiled in a tight little half-moon-shaped body lying against the nuclear membrane. In a male cell the single X uncoils, so there is no Barr body. A girl with Turner's syndrome will have no Barr body, while a man with Klinefelter's syndrome will have one Barr body. The trisomy-X female can be recognized by the presence of two Barr bodies.

Many body cells contain Barr bodies, but one of the easiest places to obtain cells to detect their presence is from inside the mouth. A little scraping of the inside of the cheek will produce hundreds of cells that can be placed on a microscope slide, stained, and studied. The Barr body, if present, will stain darkly when basic stains with an affinity for DNA are used. For screening newborns it is now common practice to examine the fetal membranes. A small piece of the amnion can be mounted on a microscope slide, stained, and studied. In this way abnormalities of the sex chromosomes can be determined within a few hours after birth. The large

Wharton jelly cells that are abundant in the umbilical cord show such bodies very well. These cells swell when they come in contact with air and so help to seal the cut ends of the umbilical cord.

Drumsticks in Leukocytes. Certain types of leukocytes, the **granulocytic polymorphonuclear cells,** also show a sexual distinction. These cells have two or three lobes to the nucleus, but in the normal female these cells have a drumstick-shaped body extending from one lobe. The number of drumsticks is one less than the number of X chromosomes in the cell, so this drumstick must represent a coiled X.

Fluorescent Y Chromosomes. Barr bodies can be used in diagnosing abnormalities of the X but will not reveal abnormalities involving the Y, such as the XYY syndrome. When cells are stained with certain acridine dyes, however, and then viewed under the ultraviolet microscope, male cells will all have a bright glowing body that is lacking in female cells. This body proved to be the Y chromosome. We have mentioned the fact that the Y chromosome carries very few genes, and its so-called **heterochromatic region** (which is inactive) glows. The bright part of the Y can be seen in interphase cells as well as in cells during mitosis or
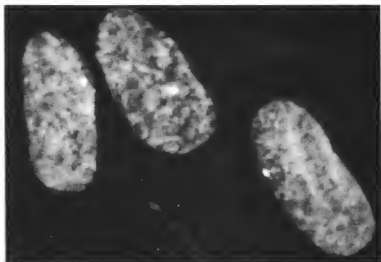

Fig. 8–8. Wharton jelly cells from the umbilical cord of a male baby showing the fluorescent Y chromosome. The bright spot in each cell represents the Y.

meiosis. To test the genetic makeup of a newborn baby the tip of the cut umbilical cord is pressed against a slide. The cells that adhere to it, known as Wharton jelly cells, are then stained and examined with the fluorescent microscope. The number of Y chromosomes is equal to the number of bright bodies that can be seen.

Those competing in women's events in international games are now tested for a Y chromosome. This is done from cells scraped from the mouth or from the follicle at the base of a hair from the head. This custom was initiated when it was found that a Polish woman athlete had a Y. She had a gene for androgen insensitivity (described later) and could not respond to the output of male hormone from testes that were in her body. As a result, she had all the external physical features of a female. At the Forest Hills Women's Tennis Association matches in 1976 a man who had undergone a sex-transforming operation insisted on competing as a woman and thus challenged the exclusion of a person because of a Y.

SEX HORMONES

The role of chromosomes in sex determination has been well demonstrated, yet we also know that sex hormones have a powerful influence on sex. A boy who is castrated before puberty will never develop the beard, voice, musculature, nor the desire for relations with women that characterizes men who have a normal output of male hormones from their testes. An overproduction of sex hormones or the administration of extra sex hormones will result in precocious sexual development in vertebrate animals.

Sex Reversal. Sometimes females of the domestic fowl will undergo an apparent change of sex. Hens that have laid eggs and brooded chicks for years may begin to develop the head furnishings and feathering of a rooster and even try to mate with other hens. An internal examination will show that the ovary (in birds only one ovary develops) has been destroyed by disease and the rudimentary testes, which have been there all the time, have enlarged and have begun to produce male hormones. Partial sex reversal can also be induced by removing the ovary from a young chick and administering male hormones. The result will be a rooster by all signs of external appearance, but it will be sterile.

Fig. 8-9. Effect of male hormone on development of sexual characteristics in young chicks. Both of these are six-week-old females. The one below was injected with testosterone at one week and has not only developed male characteristics, but they have developed much earlier than would be the case in an uninjected male.

Older women sometimes show a partial sex reversal as a result of a similar deterioration of their ovaries and an increased output of male hormones from the cortex of the adrenal gland or from their rudimentary testicular tissue. Also when women are given male hormones to slow the growth of cancer, they begin to express some male characteristics.

Quite a number of men and women have chosen to be transformed into the opposite sex. One of the first to take this drastic step was George Jorgensen, who felt that he was psychologically female. He went to Denmark, had his testes removed, and by taking female hormones achieved a degree of reversal of sex. The transformation would have been even greater had it been performed before puberty.

Relationship between Chromosomes and Hormones. How can we correlate these two forces that both influence sex? Young mammal embryos are alike regardless of their eventual sex. They possess a pair of ovotestes having an inner mass of testicular tissue and an outer covering of ovarian tissue. Eventually, one portion of the gonads begins developing at the expense of the other, in humans at about seven weeks after fertilization. If the embryo is to become a boy, the testicular part enlarges, while the ovarian tissue remains undeveloped. If the embryo is to be a girl, the ovarian part enlarges, but the testicular part remains rudimentary. The hormone output of the tissue that enlarges causes the sex organs of one sex to develop, while those of the opposite sex are inhibited.

The sex chromosomes apparently trigger the development of one type of gonadal tissue and the hormones do the rest. Hence, although sex is determined from the time of conception, it is not until the hormone output begins that sexual differentiation is noticeable.

SEX INTERGRADES

Various mixtures of male and female characteristics in one animal may occur from time to time as a result of abnormalities of sex chromosomes or hormones.

Vertebrate Intersexes. We have already shown how a balance of the male- and female-determining genes in *Drosophila* can re-

sult in an intersex, an individual having characteristics of the two sexes. Many simpler forms of animal life are normally **hermaphroditic**, each animal having sex organs of both sexes. In the vertebrates, which normally all have separate sexes, occasional hermaphrodites are seen. The gonads of such animals usually contain both testicular and ovarian tissue. Some hermaphrodites have a testes on one side and an ovary on the other; others have various mixtures of tissue in the individual gonads. The exact cause of this condition is not known, but it may be due to a double fertilization of an egg with both an X and a Y sperm. Another possibility is that two embryos of opposite potential sex have become fused. Other causes, both genetic and environmental, are possible.

Sex Mosaics. In invertebrate animals there are no sex hormones to distribute the sex characteristics evenly over the body. Instead sex seems to be determined for each cell according to the chromosomes it carries. In *Drosophila* studies individuals are found that are **gynandromorphs**. (The word is sometimes shortened to **gynander**.) The most striking of these is the bilateral sex mosaic, which is male on one side and female on the other. Such flies begin with the XX combination, but during the first mitosis, or cleavage,
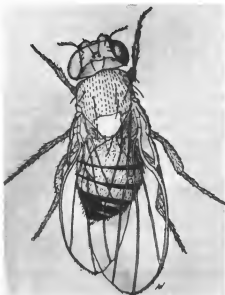

Fig. 8–10. A Drosophila gynander, bilateral sex mosaic. Sex determination in insects is cell by cell so a loss of an X in the early embryo has resulted in male development on the left, while the XX tissue on the right is female.

of the zygote one of the X chromosomes lags behind and fails to be included in the nucleus of one cell. Lost in the cytoplasm, this X disintegrates. The result is one cell with XX and one with X. The side of the body that in *Drosophila* grows from the XX cell will be female and the side that develops from the X cell will be male. If the X chromosome is lost in later cleavages, there would be smaller areas of male tissue.

Vertebrate gynandromorphs are not possible because the sex hormones are distributed throughout the body and there can be no isolated areas that are male while other areas are female.

VARIATIONS IN THE SEX RATIO

In those species with the chromosome method of sex determination we would expect an equal number of male and female zygotes. Still, if we tabulate the number of males and females in a sample population, we often find a deviation from the 1:1 ratio.

In Insects. If you collect many grasshoppers you will find that the females greatly outnumber the males. The reason seems to be that the males are less hardy than the females and many more die in early life.

In working with *Drosophila* you may make a count from a vial at one time and find a significant excess of females and at another time find the males to be in excess. This is because in the larval and pupal stages the females develop faster and emerge as adults sooner than the males. In later counts the males have probably caught up. Some cultures, however, show a consistent excess of one sex or the other, and sex-limited genes may be responsible. These will cause death of one sex but not the other. The number of males will be reduced if a male carries a recessive X-linked lethal. Such a gene will kill half of the males but none of the females.

In Humans. Some human families include a large number of girls while others have primarily boys. Generally this situation is due merely to chance variation. Sometimes, however, sex-limited lethal genes may be involved. Also, a gene is known that actually causes a reversal of sex. A dominant sex-limited gene interferes with the absorption of the male hormones, androgens. In an XX female it has no effect, but in an XY fetus testes develop and put out androgens, but the body cannot respond to it. As a result, the

fetus grows into a phenotypic female, but there will be no uterus. Some female hormones are produced by males, and these can help bring out the female secondary characteristics. Women carrying this gene will average a ratio of 3 girls:1 boy.

The overall proportion of sexes in live births in the United States is about 106 males:100 females. A survey of the sex of spontaneously aborted fetuses that are old enough to show distinctions of the sex organs also show an excess of males. This would seem to indicate a higher rate of fertilizations by Y sperm. Perhaps the Y sperm is somewhat smaller because of the smaller size of the Y as compared to the X and have an advantage of penetration of the corona around the egg. By the use of the Barr body technique, however, an excess of females has been found in embryos aborted too early to be identified by sex organ differences. Hence fertilization by X and Y sperm may be about equal after all.

From the time of sex organ development on up into old age, however, the males have a reduced chance for survival as compared to females. By age 50 women outnumber men by about 100:85, and at age 85 there are about twice as many women as men.

Reason for Differential Survival. Why do females have a survival advantage? Physiological differences may be one reason. Male hormones give men a higher rate of metabolism and greater aggressiveness so they are more likely to have heart attacks and other troubles during their middle years. Still, the differential extends down to childhood when there is no great physiological difference between the sexes. One factor might be that males are haploid for genes on the X chromosomes, of which they have only one. Since most harmful genes are recessive, in females such genes can be covered by dominant alleles on their second X, but in males all these genes are expressed. In times of stress males with such harmful traits will not survive as readily as those who do not have them. Also, many recessive lethals may be on the X, and they will cause death of any male that receives one from the mother; but females can never be homozygous for X-linked lethals because their fathers cannot carry them.

Heterozygote superiority can also give an advantage to females. Some cases are known where the heterozygote is stronger and better adapted for survival. Females can be heterozygous for X-linked genes, but males cannot.

PROBLEMS

1. How can sex transformation occur in bacteria?

2. Occasionally a *Bonellia* worm is found that is an intersex. Explain how this condition might have come about.

3. How does the role of the Y chromosome in *Drosophila* compare with that in man?

4. Assume that nondisjunction of the sex chromosomes occurs during the first meiosis of human spermatogenesis. Show the results when the sperm that are produced fertilize normal eggs.

5. Occasional tetraploid *Drosophila* are found. What sex would you expect from a fly that was AAAAXXXY; from AAAAXXYY? Explain your answer.

6. A human karyotype shows one X and half of another X. What would you expect in the way of sex abnormalities in this person?

7. If an old, sex-reversed hen should prove to be fertile as a male, what proportion of sexes would you expect from matings with normal hens?

8. It is sometimes said that drone bees have a grandfather but no father. Explain this statement.

9. Routine checks of cells from newborn babies reveal the following number of Barr bodies: one Barr body, baby reported as a male; two Barr bodies, baby reported as a female; no Barr bodies, baby reported as a female; one Barr body, baby reported as a female; two fluorescent bodies, baby reported as a male. What sex and what abnormalities of sex would you predict for each baby?

10. At a carnival show a person is exhibited as a sex mosaic—man on the right side and woman on the left side. At another show a person is exhibited who is purported to be a hermaphrodite with organs of both sexes. Do you think either or both of these is authentic? Explain your reasoning.

11. Records show that there is a higher percentage of boys among the firstborn than among the sixthborn of women in the United States. Give a plausible explanation for this.

9. HEREDITY INFLUENCED BY SEX

The chromosome differences between the sexes can influence the pattern of inheritance in a number of ways. Such influences will be explored in this chapter.

X-LINKED GENES

Most of the genes on the X chromosome have no alleles on the Y, so females are diploid and males are haploid for these genes. The pattern of transmission of such genes is different from that for genes on the autosomes. Because they lie on the X chromosome, these genes might be called X-linked genes, but since their transmission is related to sex, they are also referred to as sex-linked genes. In those forms of life with the ZW method of sex determination the sex-linked genes are on the Z chromosome and may also be called Z-linked genes.

Discovery of X-linked Genes. In the early days of studies on *Drosophila* at Columbia University by T. H. Morgan and his co-workers, literally millions of flies were examined. Occasionally the researchers would find a fly which showed inherited deviation from the parental type that could not be explained by Mendelian inheritance. Such deviations were the result of mutations. One of these mutations caused a fly to have white eyes instead of the normal red. The researchers obtained several of these white-eyed flies through inbreeding and noticed an unusual method of inheritance.

A white-eyed female mated with a red-eyed male gave white-eyed male offspring and red-eyed female offspring. Morgan reasoned correctly that the gene for white eyes must be on the X chromosome. Assuming that the gene for white eyes is recessive, the female parent would be homozygous for the gene. All her male offspring would receive their single X from her, and it would

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Fig. 9-1. A Drosophila fruit fly with white eyes and miniature wings. These carry both sex-linked characteristics, the genes lying on the X chromosome.

always carry the gene for white. Her female offspring, on the other hand, would receive an additional X from the male parent, and that chromosome would always carry the dominant gene for red. Recessive genes on the X chromosome are expressed in males even though only one is present because there are no dominant alleles for these genes on the Y. Males are said to be **hemizygous** for such genes; they are neither homozygous nor heterozygous.

Hemophilia in Man. Hemophilia, the bleeders' disease, is a typical human X-linked trait. Although it is not common, afflicting only about one male in 10,000, its effects are so dramatic that the disease is well known. A recessive gene, *h*, is responsible. This gene causes a failure to produce a plasma protein known as **anti-hemophilic globulin (AHG)**, which is one of the elements needed for normal blood clotting. When the single X that a boy received from his mother carries this gene, he bleeds excessively from minor injuries and may even bleed to death from a more serious injury. Much of the bleeding is internal as a result of the rupture of small capillaries in the stomach or intestine, so the hemophiliac is usually weak from loss of blood. The gene was common in the royal families of Europe, apparently having arisen as a mutation in a reproductive cell that produced Queen Victoria and spread from her descendants to many other countries. Many of the male heirs to thrones in Europe were afflicted and died from excessive bleeding.
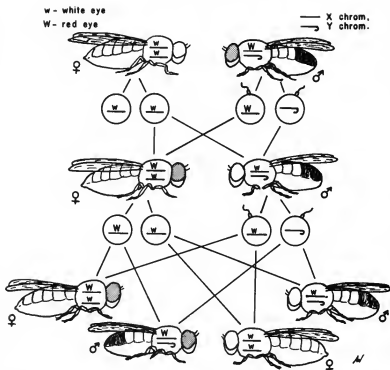
Fig. 9-2. Inheritance of the sex-linked trait for white eyes in Drosophila. Male offspring receive their single X chromosome from the female parent.

Now the disease is not the great tragedy that it once was for we can extract and administer the globulin from normal blood and thus provide for normal clotting. In fact, one boy with hemophilia recently underwent open-heart surgery, something that would never have been attempted in the past. Recessive X-linked genes show more frequently in males, but they can be expressed in a female if she is homozygous. For hemophilia this chance would be very low because the gene pool frequency is only about one in 10,000, the same frequency as the males who express the trait. Female carriers have a frequency of about one in 5000, since each female has a chance of carrying the gene on either of her two X's. Thus the chance of a marriage between a carrier female and a hemophiliac man would seem to be only one in 50 million. Half the girl babies from such a marriage would receive the gene from both parents,

Fig. 9–3. Hemophilia, the bleeders' disease, is a sex-linked human trait. This boy has the gene on his single X and a small break in a blood vessel under the skin of the eyelid resulted in extensive bleeding. (Courtesy J. V. Neel.)

so the chance for female hemophilia would appear to be about one in 100 million female births. Actually, this fails to take into account the many male deaths from hemophilia before maturity. If only one in four boys with hemophilia mature, marries, and has children, the chance for a hemophiliac daughter jumps to one in 400 million.

This calculation, however, assumes random mating. If the gene were present in a region with a high degree of intermarriage, the chance of its becoming homozygous in a female would be greatly increased. One pedigree from families in northern England showed five girls with hemophilia. There was much close intermarriage, and 13 boys also had the disease out of a total of 62 persons. Some have thought that a girl could not live beyond puberty if she had hemophilia because of excessive bleeding during her menstrual period, but these five lived to maturity and some even bore children. Perhaps in this case a milder form of the disease was involved. There is the classical form of hemophilia, **hemophilia A**, as already described. Another X-linked gene is responsible for a deficiency of a different plasma component and causes **hemophilia B**, or **Christmas disease**, which is milder in its effect. In **pseudohemophilia** an autosomal gene interferes with the breakage of blood platelets, which contain a substance that initiates clotting.
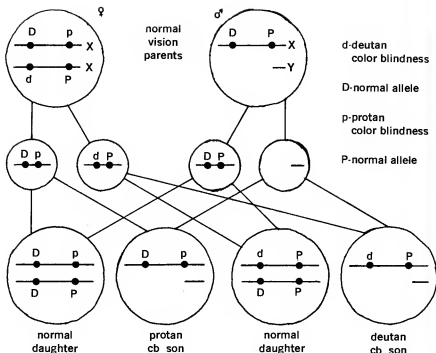
Fig. 9-4. Pedigree showing transmission of hemophilia in the royal families of Europe. Beginning with Queen Victoria, it spread to other nations because of intermarriage in royal families. (From Winchester, Genetics, Houghton Mifflin.)

Another autosomal gene causes **afibrogenemia,** a failure to produce fibrinogen, the plasma protein that forms the fibrin of the clot. The latter two diseases can be present equally in girls and boys but are rarer than hemophilia A.

Color Blindness. About 8% of the males in the United States have difficulty distinguishing red from green, but less than 0.5% of the females have this difficulty. The retina of the eye contains cones, receptor cells that are sensitive to various colors, some to red, others to green, and still others to blue. At first, only one recessive X-linked gene appeared to cause red-green color blindness, but more delicate tests showed that two gene loci are involved. The most common of these produces **deutan color blindness,** in which the green-sensitive cones are defective. About one-fourth of all cases of color blindness, however, are of the **protan** type, which is due to defects in the red-sensitive cones. Both types cause difficulty in distinguishing red from green. The two types can be recognized by proper testing.

Both genes exist in two varieties, one responsible for extreme color blindness and the other for a less severe type. People possessing the gene for **deuteranopia** have cones practically insensitive to green and experience difficulty with traffic lights. The other gene at this locus causes **deuteranomaly,** in which green can be detected if the color is bright and there is a bright light. Similar

Fig. 9–5. When a woman is heterozygous for both types of color blindness, all her sons will be color-blind, half with the deutan and half with the protan type.

variations at the other X chromosome locus cause **protanopia** and **protanomaly**. A woman can be heterozygous for both genes and have normal vision, but all her sons will be color-blind, half having the protan type and half having the deutan type.

We can show mathematically that genes at two separate loci are involved. If only one locus were involved, we would expect 0.64% of the girls to be color-blind. Since 8% of boys are color-blind, then the girls would be expected to be $0.08 \times 0.08 = 0.0064$. Statistics show, however, that fewer than this number of girls are color-blind. If two loci are involved, then the girls who would have deutan color blindness would be $0.06 \times 0.06 = 0.0036$. Girls having protan color blindness would be $0.02 \times 0.02 = 0.0004$. Adding these two frequencies to find the chance that a girl will have either of these two difficulties, we get 0.004, or 0.4%. This figure agrees with what is actually found.

Frequency of Expression of X-linked Genes according to Sex. Some recessive X-linked genes appear only in males. In

pseudohypertrophic muscular dystrophy the boys are normal during the early part of their lives, but at an average of about six years of age their muscles begin to swell, then progressively deteriorate until the victim is almost literally skin and bones. Death usually comes in the early teens. This disease results from the presence of a single recessive X-linked gene. Since such boys do not reach adulthood, they never have children, so it is not possible for a girl to receive the gene from both parents. This type of muscular dystrophy, therefore, is never found in girls, although they can be carriers. Another type of dystrophy is caused by an autosomal gene and thus can occur in both sexes equally.

Dominant X-linked genes, which are rather rare, will be expressed twice as often in girls as in boys. **Defective dentine** in the teeth results from such a gene. The dentine, which makes up the major part of the teeth, is soft and wears down easily. By twelve years of age, the teeth will be worn down to mere stumps barely protruding from the gums. In one tribe of Indians in South Dakota about 2% of the boys and 4% of the girls were found to have such defective dentine. This ratio is what we would expect since a girl, with two X chromosomes, has twice the chance of receiving the gene.

In *Drosophila* the X-linked gene for bar eye causes the eye to be shaped like a bar. In males hemizygous for this gene the eye is reduced to a narrow band. Heterozygous females have wide bar, which is halfway between narrow bar and the normal-shaped eye, so we can classify this as an intermediate X-linked gene. Homozygous females have narrow bar similar to that of the males. In any large, mixed population where the genes for bar are likely to be present, bar-eyed females will outnumber bar-eyed males by about two to one.

Attached X Chromosomes. Some female *Drosophila* have attached X chromosomes. The two X's are joined at one end so that they move together as a unit in meiosis. Hence nondisjunction in oogenesis always occurs, with some eggs having the two attached X's and some having no sex chromosomes. When such females are mated, the male offspring all receive the single X of the male parent. Hence all the X-linked genes of a male are expressed in all his male offspring. A white-eyed male crossed with a red-eyed homozygous female will have offspring that will be white-eyed if male and red-eyed if female. This is contrary to the usual pattern in which male offspring receive none of the X-linked genes of the

Fig. 9–6. Model showing attached X chromosomes in Drosophila. *Even though a Y is also present, this would be a fertile female. Such females have female offspring with sex-linked characteristics like themselves and male offspring with sex-linked characteristics like the male parent.*

male parent. These attached X females are of value when one wishes to perpetuate a particular combination of genes that lie on the X chromosome of a male.

Sex Linkage in Other Types of Sex Determination. In animals with the XO method of sex determination there is no difference in the method of transmission of genes on the X chromosome. The pattern is the same as that in the XY method. Since the Y is almost devoid of genes anyway, it makes little difference in heredity whether it is present or not.

In animals with the ZW method the sex-linked genes lie on the Z chromosome, and the females are the hemizygous sex. Barred feathers, as found in Plymouth Rock chickens, may be used to illustrate such sex-linkage. Barred feathers result from the action of a dominant gene and nonbarred from its recessive allele. A barred female crossed with a nonbarred male produces offspring that will be barred if male and nonbarred if female.

In insects with the honeybee type of sex determination, all genes

are hemizygous in the males and all behave as if they are sex-linked. Drone bees receive no genes from the male parent; all their chromosomes come from the female parent. The females, however, have biparental inheritance.

THE SINGLE ACTIVE X PRINCIPLE

It will be recalled from our study of sex chromosomes that in certain vertebrates one of the female's X chromosomes remains coiled during interphase (see chapter 8). This chromosome forms a condensed mass of chromatin known as the **Barr body**. Genes on such a tightly coiled chromosome do not function. It is only when they are in the form of a very long thin thread in interphase that they can direct the activities of the cells, a topic discussed more fully in chapter 14. Hence in animals that have Barr bodies the females are mosaics; in half of their cells one X will be uncoiled and functional, while in the other half the other X will function.

The Lyon Hypothesis. The single active X principle was first demonstrated by Mary Lyon and was based on studies of the sex-linked genes involved in coat color of mice. Females heterozygous for sex-linked genes for coat colors are mottled. Lyon reasoned that one of the X's is inactivated and forms the Barr body early in embryonic development; in all cells descending from these early cells the same X will be inactivated. These females are mosaic, having islands of cells expressing the genes on one X and other islands of cells expressing those on the other X. The tortoiseshell coat pattern in cats was found to be the result of early inactivation of the X in females heterozygous for the X-linked alleles for black and yellow. Hence it is not possible to get a tortoiseshell male, except in the rare XXY (Klinefelter's syndrome) cats.

In Human Beings. In human beings the inactivation seems to occur at about 16 days after conception, since no Barr bodies can be detected in younger embryos. By this time the embryo consists of hundreds of cells, so the mosaic islands of a woman are relatively small. Still, there are cases where a harmful X-linked gene for which a woman is heterozygous is expressed in many cells of her body. Women who carry the gene for hemophilia, for instance, show considerable variation in blood clotting time. In those in whom clotting is prolonged the X chromosome carrying the normal allele was apparently the one inactivated in the majority of the

cells. Similarly women heterozygous for either type of color blindness may have almost normal color vision or patchy color blindness in which certain areas of the retina have poorly developed cones.

Further evidence has been obtained by study of individual cells. One recessive X-linked gene causes a deficiency in the production of a red blood cell enzyme known as **G6PD (glucose-6-phosphate dehydrogenase)**. When this gene is expressed, the person will develop severe anemia as red blood cells are destroyed when he eats fava beans or takes certain drugs. A study of the blood cells of women known to be heterozygous for this gene showed that about half the cells can produce the enzyme and the other half cannot. The exact proportion varies somewhat in different women because of the chance inactivation of the X's in the early embryo.

Dosage Compensation. In each cell why are all X chromosomes except one inactivated? Genes within cells bear a certain dosage relationship to one another. When this dosage is upset, abnormalities can result (see chapter 13). Males in animals with XY sex determination have only one X, so they are haploid for the genes on this chromosome. In a normal male the dosage of one haploid set of X-linked genes apparently balances with a diploid set of autosomal genes. The normal female is diploid for X-linked genes. However, if one of her X chromosomes is inactivated, there will be the same proportion of functioning genes in female cells as in male cells. This concept is known as dosage compensation.

In organisms that do not have Barr bodies, other mechanisms of dosage compensation must operate. None of the invertebrates have these bodies. In *Drosophila* the mechanism seems to be a differential activity of genes on the X chromosomes. Studies show that the output of certain enzymes, such as tryptophan pyrolase (which influences the production of eye pigments), is the same in both sexes even though the females have two genes for the enzyme and the males have only one. Something must restrict the activity of the genes in the females so that each gene functions at only one-half the rate of the single gene in the male. It appears that dosage compensation genes on the X chromosome prevent excessive production of products when two genes are present. The product is thus held down to the same quantity as when a single gene is present. (This topic is considered more fully in chapter 14.)

Another question remains to be answered. If one X is inactivated when two are present, then why is there a difference between

an XO and an XX female? Both have one active X. Also, why is XXY different from XY? Two possibilities have been suggested. One is that the extra X may influence the embryo before Barr bodies are formed, even though there is no sign of the effect until the seventh week. The other possibility, arising from recent cytological and breeding investigations, is that a small part of the X in a Barr body is not inactivated. This part may hang out from the Barr body and uncoil so that the genes can function. These genes may be related to sex determination.

GENES ON THE Y CHROMOSOME

We have emphasized the fact that the Y chromosome contains very few genes. The few that are present fall into two categories: the incompletely sex-linked genes and the Y-linked genes.

Incompletely Sex-linked Genes. Since the X and the Y chromosomes pair in meiotic synapsis, we know that there must be allelic genes on these two chromosomes because only those regions of chromosomes with allelic genes are attracted to one another during synapsis. The region of XY synapsis is very small; in fact, the two chromosomes appear to have an end-to-end junction in human beings. These genes are known as incompletely sex-linked genes.

In *Drosophila* the recessive gene for bobbed bristles, *bb*, appears to be such a gene. In homozygous flies the bristles appear as if they had been cut off about halfway down. The gene has been located near the end of the short arm of the Y and near the end of the X where the centromere is attached. This is the region that pairs with the X during the first meiosis. The pattern of inheritance is the same as for autosomal traits, since both males and females are diploid, and it is only through linkage tests that we can demonstrate that the gene lies on the homologous portions of the X and Y. In human beings a number of traits have been suggested as being incompletely sex-linked, but evidence has not yet confirmed any of these.

Y-linked Genes. Some genes must be on the nonhomologous portion of the Y chromosome. These would be passed from a male parent to all male offspring, but never to any female offspring. Such genes would be haploid and would be expressed in each generation. The fluorescent microscope shows that most of the Y does not carry genes, so the number of Y-linked genes would not be

large. Because XO males in *Drosophila* are sterile, a gene or genes for male fertility must be on this nonhomologous portion of the Y. Some studies indicate that there are two such genes.

In humans Y-linked (or holandric) inheritance has been proposed to account for certain pedigrees in which all the boys but none of the girls showed a trait possessed by the father, a trait that has been passed on to grandsons through the sons but never through the daughters. Most of these cases that seemed to have been Y-linked, however, appear to have been merely chance distribution of genes located on an autosome. **Hairy pinna,** long hairs growing from the ears, is a trait discovered in some families in India that seems to have good support for being Y-linked. Further evidence is needed, however, before final conclusions are drawn.

SEX-LIMITED GENES

Many genes exert their effect on only one sex, although they are carried by both. It is the sex hormones that determine whether or not one of these genes is expressed. Sex-limited genes are not X-linked; in fact, the great majority are located on the autosomes.

In Domestic Cattle. Many breeds of domestic cattle have been bred for high milk yield. Breeders have learned that it is not enough to select only cows with high milk yield for breeding. Bulls have just as much to do with the milk yield of the offspring as cows. A bull may be a fine physical specimen, but he may carry genes that reduce the milk yield of his offspring. Other bulls may consistently sire female offspring who have a greater milk yield than their female parents. Hence it is customary to keep careful records and use bulls with genes for high milk yield.

In Butterflies. In the clover butterfly the males are always yellow, but the females may be either yellow or white. White is expressed in females when a certain dominant gene, W, is either heterozygous or homozygous; otherwise they are yellow. Males, on the other hand, will be yellow even though they carry the gene W. Gynanders have been found that carry the dominant gene for white; these are white on the female side and yellow on the male side. In such animals that do not have sex hormones the sex chromosomes within each cell apparently create conditions that allow sex-limited genes to be expressed.

In Birds. The striking sexual dimorphism in birds indicates the

extent of the influence of sex-limited genes. The peacock has genes for the long, colorful tail feathers, but these genes are expressed only when the bird has the male hormones. The pattern of feathering in the domestic fowl illustrates an interesting example of sex-limited genes. A recessive gene, h, when homozygous, causes the cock feathering in the males of most breeds of these chickens. The gene has no effect on the females, and they are all hen-feathered. In some breeds, however, such as the Hamburgs, some of the males are hen-feathered. In this breed there are some genes for hen feathering, H. When males receive one or two of these genes they will be hen-feathered. Still other breeds, such as the Sebright bantams, have hen feathering in both sexes. These are all homozygous for the gene that causes hen feathering, HH. The possible genotypes and phenotypes would be:

Genotype	Female Phenotype	Male Phenotype
HH	Hen-feathered	Hen-feathered
Hh	Hen-feathered	Hen-feathered
hh	Hen-feathered	Cock-feathered

We can show the influence of sex hormones on the expression of these genes in breeds where the females are all hen-feathered and the males are all cock-feathered. Castration of the male results in a hen-feathered bird. Castration of the female and administration of the male hormone produces a cock-feathered bird. Thus it appears that the male hormone is necessary for the expression of the gene for cock feathering.

In Human Beings. Many sex-limited genes are present in human beings. The genes for the male beard, male voice, and male musculature are normally expressed only when the male hormones are present. These latent genes in a woman can be expressed if she is given male hormones, as in cases of cancer treatment. On the other hand, the genes for the size and shape of the breast are typically expressed only in females, although a girl inherits this trait just as much from her father as from her mother. The size, shape, and other characteristics of the primary sex organs are among the other characteristics that depend on the action of sex-limited genes.

SEX-INFLUENCED GENES

This category includes genes that may be expressed in both sexes but are so influenced by sex that they act as dominants in one sex and recessives in the other. A higher threshold of gene activity is required for their expression in one sex than in the other.

Coat Color in Cattle. Ayrshire cattle are all spotted, but some have red spots on white while others have mahogany spots on white. The mahogany and white coat is due to a gene that is dominant in males and recessive in females. For such genes it is customary to use the first letter of the characteristic that is dominant in males, so we should choose M as the gene symbol. Homozygous MM cattle are mahogany and white regardless of sex, and homozygous mm are red and white regardless of sex. The heterozygous Mm, however, are mahogany and white if males and red and white if females.

Horns in Sheep. A similar condition is found for horns in sheep. Dorset sheep have horns in both sexes, whereas Suffolk sheep do not have horns in either sex. The Dorset are homozygous for the genes for horns, H, and the Suffolk are homozygous for the allele, h. When the two breeds are crossed we find that all the male offspring have horns and all the female offspring are hornless. This shows that the gene for horns is dominant in the males and recessive in the females.

Length of Index Finger in Humans. If the hand is placed on a sheet of paper with the fourth finger touching a horizontal line, the index finger will fall short of the line in some people and touch it or exceed it in others. The long index finger is more common in females, and statistics indicate that the gene that influences this trait may be dominant in females and recessive in males. Since the total length varies, other genes must be involved; variations in embryonic development may also play a part.

Baldness. Pattern baldness has also been mentioned as a possible sex-influenced trait that is dominant in men and recessive in women. Several genes must be involved, however, since there is considerable variation in the pattern and degree of baldness, and there is some evidence that these genes may be more of the sex-limited than sex-influenced type. Some men with a low degree of masculinity who are being treated with androgenic hormone will begin to lose their hair. A certain hormone level must be present for this trait to be expressed.

PROBLEMS

1. White eyes in *Drosophila* results from a recessive X-linked gene. Give the expected results from a cross of a heterozygous red-eyed female and a white-eyed male.

2. Several cases of hemophilia in women were reported in England. One such woman marries a normal man. Show the genotype and phenotype of parents and possible children of such a marriage.

3. A color-blind man marries a woman with normal vision who had a color-blind father. Show the expected children. (Assume that the deutan type is involved.)

4. Parents with normal color vision have four sons. Tests reveal that two of these boys have deutan color blindness and two have protan color blindness. Show the genotype of both parents. Also show the genotype of any daughters they may have.

5. Optic atrophy (blindness due to atrophy of the optic nerve) results from a recessive X-linked gene. A woman with this trait marries a normal man, and their first child is a daughter with albinism, which is a recessive autosomal trait. What is the chance that their next child will be a son with optic atrophy and normal
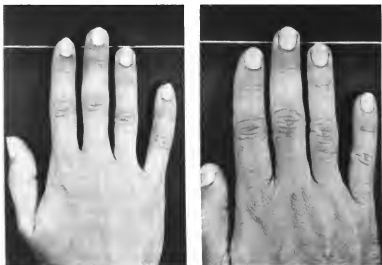
Fig. 9–7. The index finger of some people is longer than the fourth finger, as in the left, and shorter in others, right. This seems to be a sex-influenced trait, with the long index finger being dominant in females and recessive in males.

pigmentation; a daughter with optic atrophy and normal pigmentation; a son with both albinism and optic atrophy?

6. In cats the genes for yellow and black are alleles that are intermediate and X-linked. The heterozygote has a combination of yellow and black known as tortoiseshell. Show the offspring that would be expected from a cross of a tortoiseshell female with a yellow male.

7. Barred feathers in the domestic fowl develop as a result of the action of a dominant X-linked gene. Show the offspring expected from a cross between a barred hen and a nonbarred rooster.

8. The human Xg blood antigen results from a dominant X-linked gene. Those having the antigen are Xg positive while those lacking it are Xg negative. On a certain island in the South Pacific 30% of the men are Xg positive. What percentage of the women would be expected to be Xg negative?

9. A woman shows a considerable degree of deutan color blindness, yet her father has normal color vision. How could you explain this?

10. A mahogany and white cow is mated with a red and white bull. Show the color of the offspring from such a cross.

11. When two hornless sheep are mated, about half of the male offspring from many crosses have horns while all the females are hornless. Show the genotype of the parents.

12. Chartreuse eye color in the honeybee is recessive to the wild-type brown eye color. A brown-eyed drone mates with a queen with chartreuse eyes. Show the genotype of these two and the genotype and phenotype of their offspring.

13. Suggest a biological reason why the nonhomologous portion of the Y chromosome does not carry many genes.

14. A woman with a short index finger marries a man with a long index finger. Show the expected index finger length in their children.

15. A man with no hair growth on his chest has six sons who all have very hairy chests. Give a possible explanation for these results.

10. MULTIPLE ALLELES AND POLYGENIC INHERITANCE

Most of the genes used thus far to illustrate genetic principles have been assumed to exist in only two alternate forms. In *Drosophila* we have considered a recessive gene for vestigial wings and its dominant alternate allele for normal wings. In humans we have considered a recessive gene for albinism and its dominant allele for normal pigmentation. We know, however, that there are other genes which cause variations in wing characteristics in *Drosophila* and other genes which affect skin pigmentation in man. In this chapter we shall consider some examples of these multiple variations in genes.

MULTIPLE ALLELES

We could never know of the existence of a particular gene and how it functions unless we found an allele that causes a different phenotype. For instance, we could not know that there is a gene at a particular locus on a chromosome in mice which contributes to normal hair growth had we not discovered an allele that causes hairlessness. These variant alleles typically arise by mutation of the wild-type or normal genes, so we often refer to them as mutant genes. There is no reason to assume that only one kind of mutation can arise from a wild-type gene or that mutant alleles themselves cannot mutate to still different alleles. Recall that in the case of the X-linked genes for color blindness and hemophilia more than two alleles can exist for the same locus on the X chromosome. These are known as multiple alleles.

The White-Eye Series in *Drosophila*. A classic example of multiple alleles is to be found in a series of alleles that affect eye color in *Drosophila*. In the early days of research on this fruit fly at Columbia University T. H. Morgan found a male with white

eyes that proved to result from a sex-linked mutant. The normal wild-type allele contributed to the production of red eyes. The symbol w was used to represent this mutant gene and W to represent its normal allele. (More recently geneticists have tended to use the symbol w^+ for the wild-type allele.) Later another sex-linked, recessive mutant was discovered for eosin eyes, a light orange-red color. When an eosin-eyed male was crossed with a white-eyed female the male offspring had white eyes, as expected, but the heterozygous females had eyes intermediate between eosin and white. The male offspring of these heterozygous females were half eosin and half white. Thus it appeared that the genes for eosin and white were alleles. The gene for eosin proved to be recessive to the gene for the wild-type red. Hence this was a case of multiple alleles—three genes at the same locus of the X chromosome, although any female could carry only two of these and any male could carry only one.

This discovery raised a problem in gene symbolism. How could the principle of using the same letter for allelic genes be retained and three variants be represented? The problem was solved by using superscripts like these: use w for white, W or w^+ for the wild-type red, and w^e for eosin.

Continued investigations showed quite a number of other alleles at this locus. Some of these are listed below roughly in the order of intensity of the color of the eye from darkest to lightest.

w^+—red	w^h—buff
w^w—wine	w^t—tinged
w^{co}—coral	w^h—honey
w^{bl}—blood	w^{ec}—ecru
w^c—cherry	w^p—pearl
w^a—apricot	w^i—ivory
w^{cr}—eosin	w—white

The gene for red appears dominant to all the other alleles, but most of the other alleles show intermediate inheritance when crossed with one another. Tests of the amount of pigment in the eyes by paper chromatography, however, show that there are differences in the eyes of flies which are homozygous and heterozygous wild-type, even though the eyes appear equally red in both types. Such tests show that different strains of flies with the wild-type red eyes may differ in the amount of pigment in the eyes. Hence there must be alleles in the series that do not alter the

amount of pigment sufficiently to cause a visible difference in the color but do cause a difference detectable by chromatography. Such genes have been called **isoalleles**. The gene expression in the organism seems the same for all these isoalleles, but special techniques can distinguish differences on the cellular level.

Isoalleles Affecting Human Hemoglobin. The gene for sickle-cell anemia, Hb^s, is an allele of the gene Hb^A, which is for the normal amino acid chain in the hemoglobin molecule. A third allele, Hb^c, has been discovered that causes another variation in this chain and a milder form of anemia. Then it was found by chromatography that quite a number of other alleles cause still other small changes in the amino acid sequence of the molecule, but these did not cause anemia or any other effect on a person having these genes. Hence this latter group were isoalleles of the gene Hb^A.

Multiple Alleles in Rabbits. In rabbits gene c causes albinism, and its wild-type allele C functions in the production of full color. A third gene that causes the rabbits to be white except for color on the ears, tail, feet, and nose region has also been discovered. This pattern is known as Himalayan, and its gene symbol is c^h. Unlike the white-eye series in *Drosophila*, the gene for the Himalayan trait was found to be dominant to the gene for albinism but recessive to the wild-type allele C. A fourth allele was found that causes the fur to lack all yellow pigment resulting in a silver-gray appearance designated as chinchilla, c^{ch}. The chinchilla allele was found to be dominant to the gene for Himalayan and also to the gene for albinism but recessive to the gene for full color.

Many other cases of multiple alleles have been discovered in other forms of life including humans. The genes for the human blood types and the Rh factor fall in this category and will be considered in the next chapter.

Tests for Allelism. As a rule, all the genes in an allelic series affect the same trait, such as eye color in *Drosophila* and human hemoglobin structure. It is also known, however, that genes at different loci may affect the same trait. In chapter 9 we learned that genes at separate loci may affect color vision in humans. Hence we need some test to determine if two genes are alleles or if they are at different chromosome loci. By crossing organisms that express the different phenotypes or by studying pedigrees where such crosses have occurred, we can determine if the genes are alleles. One eye color in *Drosophila* is known as carnation, and it

is X-linked as is the gene for white. To find if the carnation is an allele of the gene for white we simply cross carnation flies with white flies. In this case the females all have the wild-type red eyes. Hence we can conclude that the two genes are not alleles. The white-eyed female fly carried the dominant normal allele (car^+) of the recessive mutation, carnation, while the carnation-eyed male fly carried the dominant normal allele of white (w^+). This is a case of duplicate recessive epistasis (see chapter 6). Had the two genes been alleles, the female offspring of the cross would have had an eye color intermediate between white and carnation, or had one of the two genes been dominant, the dominant color would have been expressed.

The dihybrid cross can be diagrammed as follows:

$$w\ car^+/w\ car^+ \times w^+\ car/Y = w\ car^+/w^+\ car \text{ (red female)}$$
$$+ w\ car^+/Y \text{ (carnation male)}$$

Had the two genes been alleles the cross would have been

$$w/w \times w^{car}/Y = w/w^{car} \text{ (intermediate female)}$$
$$+ w/Y \text{ (white male)}$$

In human beings we cannot make crosses to determine allelism, but we can study pedigrees. For instance, a man with deutan color blindness married to a woman with protan color blindness will have daughters with normal color vision. This shows that the two genes are not alleles since each parent must carry a dominant that covers the recessive of the other parent. Had the two genes been alleles, the daughters would all be color-blind, showing some degree of both red and green insensitivity.

Pseudoalleles. Chromosomes that are paired during synapsis of the first meiosis may exchange segments in a process known as crossing-over (see chapter 12). Normally the chromosomes are paired gene for gene, but in rare cases there seems to be a slight misalignment so that in crossing-over two alleles may be positioned on one chromosome and none on the other.
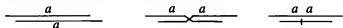
Mutations may occur in one of the two genes so that the two genes are different. These two genes still influence the same trait, but they have slightly different loci and may be called pseudoalleles. A series of four such pseudoalleles (the lozenge group) that affect the texture of the eye in *Drosophila* have been found.

Also, the Rh factor in humans shows that three such pseudoalleles may be involved.

QUANTITATIVE INHERITANCE: POLYGENES

Up to this point we have used traits with distinct qualitative differences as illustrations for most of our crosses, but it is obvious that many inherited traits show quantitative differences. Human stature is certainly influenced by heredity, yet we cannot classify people as just short or tall, as would be the case if there were simple dominant-recessive inheritance, or as short, medium, and tall, as we would with simple intermediate type of inheritance. The presence of several multiple alleles would also be an inadequate explanation for the continuous variation in human stature. Environment is certainly a contributing factor to height, but it does not contribute enough to explain the great quantitative variation. If we assume that a number of genes at different loci (**polygenes**) affect stature, however, the variation could be explained.

Color in Wheat. Nilsson-Ehle, a Swedish investigator working with wheat, obtained a number of varieties having kernels of different color. A cross between wheat with dark red kernels and wheat with white kernels gave offspring with an intermediate shade of red kernels. An *inter se* cross of this F_1 yielded five phenotypic classes of offspring with color ranging from deep red to white. The ratio was 1:4:6:4:1. Such results would be expected if two gene loci were involved in pigment production. The genes at these two loci may be **contributing** (pigment producing) or **neutral.** Four contributing genes for the red pigment would cause the darkest red, and the others would show red in proportion to the number of contributing genes present.

Number of Neutral Genes	Number of Contributing Genes	Color	Proportion
4	0	white	$\frac{1}{16}$
3	1	light red	$\frac{4}{16}$
2	2	medium red	$\frac{6}{16}$
1	3	dark red	$\frac{4}{16}$
0	4	darkest red	$\frac{1}{16}$

Note that the number of F_2 phenotypic classes of offspring exceeds the number of genes involved by one. This is a general rule for polygenic inheritance. For three pairs of alleles (a total of six genes) seven classes of offspring would be obtained. For four pairs of alleles (a total of eight genes) nine classes are expected, and so on.

Size in Chickens. An interesting case of polygenic inheritance was found by Punnett in the domestic fowl. He crossed the small Sebright bantam with the large golden Hamburg and obtained birds of an intermediate size, as he had expected. In the F_2 there was a range of size variation, again as expected, but he was surprised to find a few chickens that were larger and a few that were smaller than either of the P_1.

Punnett reasoned that there must be four pairs of genes involved in size in this particular cross. The Hamburgs must be homozygous for three pairs of genes for large size and homozygous for one pair of genes for small size. This genotype might be represented as $AABBCCdd$, if we allow capital letters to represent genes for large size. The bantams, on the other hand, could be homozygous for D, but all the other genes would be for small size. Their genotype would be $aabbccDD$. The F_1 would be heterozygous for all four of the gene pairs. The F_2, however, would include some homozygous for all the genes for large size and would be larger than the Hamburgs. They would actually have picked up a pair of genes for large size from the bantams. Conversely, a few would be $aabbccdd$ and smaller than the bantams, having picked up a pair of genes for small size from the large Hamburgs.

Plant and animal breeders often take advantage of this principle. They may cross a desirable variety with a poor variety and then, through selection, pick up some of the few good characteristics that were in the poor variety. The yield of corn has actually been increased by crossing a high-yielding variety with one that has a poor yield and then selecting for high yield. Even the poorest varieties may carry some genes that can improve those which are high yielders.

Skin Color in Humans. The amount of melanin in the skin can vary according to exposure to sunlight, but even without such exposure a considerable variation exists among the peoples of the earth. The variation in pigment is continuous, thus suggesting polygenic inheritance.

Marriages between blacks and whites produce children with in-

termediate shades of skin. Marriages between two of these intermediates can show a range of variation from the fair skin of whites to the more heavily pigmented skin of blacks. An analysis of the results of such marriages made by Curt Stern indicated that there must be at least four contributing genes for pigment deposition involved in the gene differences of the two races. This would give an expectation of the white type of skin pigmentation in one child out of 256 from a marriage of two intermediates and a like number with the full heavy pigmentation of the black race. Within races, of course, there are also variations, so other genes must be involved, but this study concentrated on the genes responsible for color differences between these two races.

Eye Color in Humans. Human eye color can be a confusing trait to study. One may learn that blue eyes result from a recessive gene while the dominant allele causes the eyes to be brown. In any large group, however, there is likely to be a person with brown eyes who has blue-eyed parents. We would think this condition should be impossible, barring the very rare instances of mutation, but it happens much too often to be caused solely by mutation. One basic recessive gene determines if there is to be any brown melanin in the iris of the eyes. Persons homozygous for this gene have blue eyes for the same reason that deep water is blue when there is no mud suspended in it. The deeper part of the iris scatters the wavelengths of light and only the blue is reflected back. When a person has the dominant allele, however, there will be melanin in the outer part of the iris, but the amount of this melanin depends on polygenes. Genes for only a little melanin will cause the eyes to be green, as some of the blue will show through the light melanin deposit. More melanin will give hazel eyes, still more will give a light brown, and heavy deposits will produce the very dark brown that we often call black. The recessive gene for blue (nonpigmented) is epistatic to all the melanin-producing polygenes, so the eyes will be blue no matter how much melanin is coded by these other genes. A man may have blue-green eyes because he has genes for very light melanin deposits, but he might refer to his eye color as blue. He might marry a blue-eyed woman, homozygous for blue, but who also carries genes for heavy melanin deposits. A child of this couple may receive the gene for pigmentation from the father and genes for heavy deposits of melanin from the mother and thus have brown eyes.

Estimating the Number of Polygenes. It is possible to esti-

mate the number of polygenes involved in any particular polygenic trait by observing the proportion of F_2 offspring that show one extreme or the other. When only one pair of alleles is involved we know that $\frac{1}{4}$ of the offspring will show either extreme, a 1:2:1 ratio. With two pairs of alleles involved the figure drops to $\frac{1}{16}$, with a total ratio of 1:4:6:4:1. For each additional pair of alleles you multiply by four to get the extremes. The figure can be obtained for any number of pairs of alleles by the simple formula $(\frac{1}{4})^n$, where n equals the number of pairs of alleles. For five pairs of alleles, for instance, this would be $(\frac{1}{4})^5 = \frac{1}{1024}$. If you study many offspring and find that about one in each 1024 shows one extreme and an equal number show the other extreme, you could conclude that five pairs of alleles must be involved in producing the trait.

Discontinuous Variation of Polygenic Traits. In general we say that polygenic traits show continuous variation from one extreme to the other, while traits due to a single pair of genes show discontinuous variation. Discontinuous traits can be separated into groups, each clearly distinguishable from the others. In some cases, however, we find discontinuous variations involving polygenes.

Sensitivity to high-energy radiation is a variable trait that is influenced by heredity. Different amounts of such radiation are lethal to different species of animals, but there is also variation within each species. J. W. Grahu found one strain of albino mice in which some would be killed by 450 rads but 570 rads were required to cause 100% lethality. There was continuous variation that could be expressed in the form of a bell-shaped curve. Another strain of black mice, however, had a sensitivity range from about 620 to 660 rads. Hence there was discontinuous variation between the two strains, even though each showed continuous variation within its own strain. Hybrids between these two strains showed an average lethality of about 565 rads, with a range of about 520 to 620. This middle range is typical of inheritance of intermediate polygenic traits. The F_2s showed a range all the way from about 450 to 660, as would be expected by segregation of the genes affecting susceptibility to radiation.

Members of the Watusi tribe of central Africa, who are noted for their towering stature, live in close proximity to a Pygmy tribe. Although there is variation within each tribe, the shortest adult Watusi is much taller than the tallest Pygmy. Thus the curves of
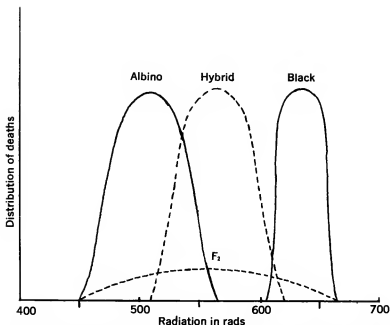
Fig. 10-1. Discontinuous variation in susceptibility to radiation in mice. All the mice in the albino strain are killed at a dose too low to kill any of the black strain. Hybrids of the two strains are between in susceptibility while the second generation shows an even greater range, as is typical of polygenic inheritance. (Data from Grahn.)

distribution of height of the two tribes do not overlap; a considerable gap exists between them. Although we lack adequate records of matings between these two tribes, we would expect any hybrids to fall within a curve intermediate between the two parents. Matings between hybrids would show a continuous variation that could extend all the way from the smaller Pygmies up to the taller Watusis.

Another example of how polygenes can be involved in discontinuous traits concerns the number of toes on the hind legs of guinea pigs. This is an either/or trait: The extra toes are there or they are not there. All guinea pigs in strain 2 had three toes, which is considered the normal number, but all those in strain D had four toes. Hybrids between these two had three toes, and in the F_2 a ratio of 188 three-toed to 45 four-toed guinea pigs was
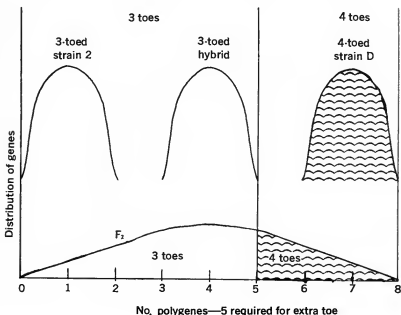
Fig. 10–2. Polygenic inheritance of a discontinuous trait, extra toes in guinea pigs. It seems as if five contributing genes are required to produce a fourth toe on the hind foot of guinea pigs. (Data from Stern.)

obtained. This 3:1 ratio was first considered to be a simple case of dominant-recessive inheritance. Further breeding, however, showed that the inheritance was more complex. Crosses of two four-toed F_2s gave some offspring with three toes, which would not be expected if four toes was a recessive trait. Sewal Wright proposed a polygenic explanation to the effect that four pairs of genes were involved. Guinea pigs in strain 2 had from zero to two genes for four toes, while those in strain D had from six to eight genes for four toes. The results of the crosses indicated that a guinea pig had to receive at least five genes contributing to polydactyly to have four toes. The F_1, with from three to five genes for polydactyly, would all have three toes. In the F_2 roughly about a fourth of the offspring would get at least five of these genes and have four toes. Many human traits that have been difficult to understand could be of a similar nature. A certain threshold of contributing genes might be required in order for the trait to be expressed.

STATISTICAL MEASUREMENT OF
POLYGENIC INHERITANCE

In evaluating the degree of variation brought about by the quantitative action of multiple genes, we often use statistical methods.

Variance and Standard Deviation. These statistical tools may be used to measure the degree of variation within a group and are particularly useful when comparing two groups. Let us use human stature, a good example of polygenic inheritance, to illustrate.

Suppose we measure the heights of a typical sample of adults in Washington, D. C. We can include both sexes but must multiply the heights of women by 1.08 in order to compensate for their smaller stature because of their sex. If we plot the heights on a graph, we will find a bell-shaped curve of normal distribution (figure 10–3). The largest number of people will be grouped around the mean, with the numbers gradually getting smaller as we approach the extremes. Suppose we find that the mean is 68
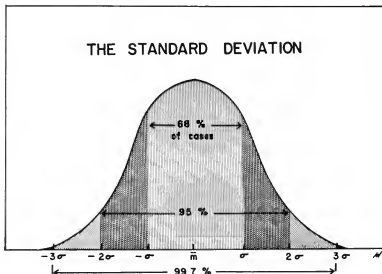
Fig. 10–3. *Distribution of events according to the standard deviation. Only about 5% of the cases will vary from the mean by more than two standard deviations.*

inches. The variance within this group is the average of the squared deviations from the mean and is represented by the formula.

$$V = \frac{\Sigma f d^2}{n}$$

The large sigma (Σ) stands for sum of, f stands for the frequency or number of persons of each height, d stands for deviation from the mean, and n stands for the total number of people measured, in this case 200.

Let us say that we obtain a variance of 9. This figure has value in comparing different populations as to their degree of variability but also has the disadvantage that it is expressed in terms of square inches and we do not measure people in square inches. We can overcome that difficulty by taking the square root of the variance to get the standard deviation, which is in inches. In this case the standard deviation (σ) would be 3. What does this tell us about the sample of people we have tabulated? We know that about 68% of them will vary no more than one standard deviation (3 inches) from the mean and about 95% will vary no more than two standard deviations (6 inches). Only about 0.3% will be at the extremes represented by more than three times the standard deviation (9 inches). See table 10–1 for other deviations. The complete formula for obtaining the standard deviation would be

$$\sigma = \sqrt{\frac{\Sigma f d^2}{n}}$$

QUANTITATIVE VARIATION IN HUMANS. These measures will show the relative degree of genetic homozygosity in a population. If we find one population with a small standard deviation and another with a large standard deviation, we can assume that the first population has more genes in common with one another, even though the means of the two may be the same. Suppose we study a group of 200 people in Nairobi, Kenya, and find that they also have a mean height of 68 inches. This mean would be the same as that for the group in Washington, but suppose the Kenyans showed a variance of 6.25 inches with a standard deviation of 2.5 inches. This would indicate that there is a greater genetic variation in the people in Washington than in Nairobi. In Washington perhaps there has been a greater degree of blending of genes from different races, while Nairobi has remained more homogeneous in its native population.

TABLE 10-1
PERCENT DEVIATIONS FROM THE MEAN ACCORDING TO
STANDARD DEVIATION

σ	Percent of Cases with Deviations This Great or Greater	Odds against Occurrence of Deviation This Great or Greater
0.6745	50.00	1.00:1
1.0	31.73	2.15:1
1.3	19.36	4.17:1
1.6	10.96	8.12:1
1.8	7.19	12.92:1
2.0 (sig.)	4.55	20.98:1
2.2	2.78	34.96:1
2.4	1.64	60.00:1
2.6 (highly sig.)	0.932	106.30:1
2.8	0.511	194.70:1
3.0	0.270	369.40:1
3.5	0.0465	2,149.00:1
4.0	0.00634	15,770.00:1
5.0	0.0000573	1,744,000.00:1
6.0	0.00000020	500,000,000.00:1

SIZE COMPARISON IN CHICKENS. As an example of how these statistical measurements may be used commercially, let us consider a study of weight of chickens after eight weeks of uniform feeding. Table 10-2 shows how the standard deviations can be calculated in a tabular form. The two breeds of chickens have about the same mean weight but with considerable variation in the standard deviations. Hence if the chicken farmer wanted to have fryers of a rather uniform weight to market, he would choose breed B because this breed is obviously more homozygous in genes related to body weight than breed A.

TABLE 10–2
SIZE DISTRIBUTION OF CHICKENS IN BREED A

Weight Range in Pounds	Midclass Value v	Number of Chickens in Each Group f	fv	Deviation of Class Value (v) from Mean d	d^2	fd^2
2.5–2.7	2.6	8	20.8	−0.4	0.16	1.28
2.7–2.9	2.8	22	61.6	−0.2	0.04	0.88
2.9–3.1	3.0	40	120.0	0.0	0.00	0.00
3.1–3.3	3.2	18	57.6	0.2	0.04	0.72
3.3–3.5	3.4	12	40.8	0.4	0.16	1.92
Σ		100	300.8			4.90

$$\overline{m} \text{ (mean)} = \frac{\Sigma fv}{n} = \frac{300.8}{100} = 3.008$$

$$\sigma \text{ (stand. dev.)} = \sqrt{\frac{\Sigma fd^2}{n}} = \sqrt{\frac{4.90}{100}} = 0.221$$

SIZE DISTRIBUTION OF CHICKENS IN BREED B

Weight Range in Pounds	Midclass Value v	Number of Chickens in Each Group f	fv	Deviation of Class Value (v) from Mean d	d^2	fd^2
2.5–2.7	2.6	4	10.4	−0.4	0.16	0.64
2.7–2.9	2.8	16	44.8	−0.2	0.04	0.64
2.9–3.1	3.0	60	180.0	0.0	0.00	0.00
3.1–3.3	3.2	14	44.8	0.2	0.04	0.56
3.3–3.5	3.4	6	20.4	0.4	0.16	0.96
Σ		100	300.4			2.80

$$\overline{m} = \frac{\Sigma fv}{n} = \frac{300.4}{100} = 3.004$$

$$\sigma = \sqrt{\frac{\Sigma fd^2}{n}} = \sqrt{\frac{2.80}{100}} = 0.1672$$

Standard Error of a Mean. This is another useful statistical tool to measure the reliability of a mean. It makes allowance for the number in the sample and the degree of variation. If only a small number has been chosen for measurement, the standard error will be greater than if a large number is used. A large number is more likely to conform to the mean for the total population. Also, if the variation is large, the standard error will be greater than if the variation is small. The standard error can be obtained quite easily once the standard deviation has been obtained. The formula for determining the standard error of a mean is

$$s_{\overline{m}} = \frac{\sigma}{\sqrt{n}}$$

The standard error of the mean of the sample of chickens in breed A would be 0.022. We can express the mean (with the standard error) as 3.008 ± 0.022 pounds. This indicates that about half the samples of this size will have a mean that will fall within one standard error of this mean and about 95% will fall within two standard errors of the mean. We can refer to table 10–1 for other possibilities as these figures refer to standard errors as well as standard deviations. For breed B the mean would be 3.004 ± 0.012 pounds. Thus even though there were 100 chickens in each sample, breed A has a higher standard error because the chickens show greater variability.

The sample of people from Washington would have a mean of 68 ± 0.364 inches, while the sample from Nairobi would have a mean of 68 ± 0.303 inches. The difference in the standard errors reflects the greater variability of the people in Washington.

PROBLEMS

1. In *Drosophila* a certain recessive mutant gene causes the eyes to be cinnabar, a bright scarlet red color, in contrast with the duller wild-type red. Another recessive mutant gene causes the

eyes to be brown. Breeding tests show both genes to be autosomal. Tell how you would determine whether or not these genes are alleles.

2. A rabbit with a chinchilla coat is crossed with one having a fully colored coat. Could both albino and Himalayan coats appear in the offspring? Could either appear?

3. In tomatoes assume that there are three polygenes affecting the size of the fruit. Homozygous *aabbcc* are the smallest and have an average fruit weight of 4 ounces. *ABC* are contributing genes, each of which adds an average of ½ ounce to the weight. Homozygous *AABBCC,* therefore, weigh about 7 ounces. Show the average weight of the offspring of a cross between a plant bearing the smallest fruit and one bearing the largest.

4. A 5-ounce tomato is crossed with a 5½-ounce tomato and among the offspring there is one plant that produces tomatoes with a weight average of about 6½ ounces. Show the possible genotypes involved.

5. In some human families parents with average IQs will have a child who will develop a very high IQ while other children of the same family will be near the average. Assuming that the children all have about the same educational opportunities, explain how this might come about.

6. A person with green eyes married to one with pure blue eyes can have a child with much darker brown eyes than a couple who both have green eyes. Explain why.

7. Holstein cattle show varying degrees of spotting as a result of polygenes. Suppose you find that the cattle can be divided into eleven different classes according to the degree of spotting. How many pairs of genes would be involved in this trait? Explain your answer.

8. The skin pigmentation of a group of people in Jamaica was evaluated with a colorimeter, and a scale of 0–78 was assigned to the degree of pigmentation in areas not exposed to sunlight. (Albinos were not included in this study.) In one marriage the wife had a skin value of 10 and the husband a value of 30. What would be the skin value of a child who had the greatest amount of melanin possible? What would be the value of one with the lightest skin possible?

9. Traditionally students have learned that blue eyes is a recessive trait with brown as the alternate dominant. The few cases

where blue-eyed parents have had a child with brown eyes, however, have caused a question about this simple explanation. One explanation was given in this chapter. Formulate another possible explanation on the basis of polygenes with a required threshold for expression similar to the one for toes of guinea pigs. Assume that genes for melanin deposit are contributing genes.

10. The number of red blood cells varies in different people. Suppose you study 64 men and find that they average 5 million red blood cells per cubic milliliter. The sum of the squared deviations (in millions) of these men from the mean is 4. What is the variance, the standard deviation, and the standard error of the mean? (Omit the six zeros and do all figuring in millions.)

11. A group of 64 women from the same population show an average red blood cell count of 4.5 million. The sum of the square of these deviations is 8. Find the variance, the standard deviation, and the standard error of the mean of this sample of women.

12. From the results in problems 10 and 11 would you say that a sample of men from this population would have a higher red blood cell count than a sample of women? *Note:* If the standard errors of the two means overlap, this is a sign that the figures do not show a significant indication of a difference between the men and women.

13. From the standard deviations of the previous problems would you say that women show more or less variation in their red blood cell count than men?

11. HUMAN BLOOD GENETICS

Human blood is a good subject for genetic study because it exhibits so many variations that are inherited regardless of environmental circumstances. Since all blood is similar in appearance it might seem a poor choice, but chemical and immunological analysis reveal many variations. So many different combinations of blood traits are possible that a person's blood is almost as distinctive as his fingerprints as a means of identification. It would be difficult to find any two persons with the same combination of blood traits, identical twins excepted. Practically all the principles of genetics can be illustrated by blood. Also, blood traits have great medical and legal significance. In blood transfusions, organ transplants, childbirth, and in cases of disputed parentage they are considered. We shall begin our study with the first distinctions discovered, the ABO blood groups.

THE ABO BLOOD GROUPS

The existence of blood groups was not known before the present century, although incompatibility of certain bloods was recognized earlier. Blood transfusions were attempted as early as the eighteenth century. Sometimes they were successful, but in other cases the recipient died. It was observed that when blood from different persons was mixed outside the body, it would sometimes blend smoothly and in other cases the red blood cells would gather together in clumps, or *agglutinate*.

Discovery of the Blood Groups. An explanation of these reactions came in 1901 when Karl Landsteiner separated blood cells from the plasma and then made various recombinations. The defibrinated plasma (serum) would always mix smoothly with cells from the donor but would sometimes cause agglutination of the

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cells of other persons. On the basis of his observations Landsteiner identified three blood types now known as O, A, and B. The rarer AB type was found later. In time the medical profession recognized the significance of these discoveries, and today blood transfusions can be given safely as long as the proper types are administered.

Antigens and Antibodies. The agglutination reaction results from the combination of antigens in the cell membranes of red blood cells with specific antibodies in the plasma. An antigen is a part of the molecule of proteins, nucleic acids, and some of the complex carbohydrates. Antigens can be identified only when they react with antibodies that are specific for them. Antibodies are plasma proteins found in the **gamma globulin fraction** of serum in the higher vertebrates. They are produced in response to the entry into the bloodstream of a foreign antigen, that is, an antigen from a source other than the animal's own body. When disease germs, such as the bacteria of typhoid fever, are introduced into the human body, certain cells of the body respond by producing antibodies against the antigens in the cell membrane of these bacteria. The invading germs might be clumped or otherwise be so affected that they can be overcome by the body. When blood serum from a person who has been thus sensitized is mixed with typhoid bacteria, these bacteria will be agglutinated. Antibodies are highly specific and will react with one antigen only. Vaccination stimulates antibody production by introducing dead or weakened organisms into the body, but we must be vaccinated for each disease to which we wish to establish immunity. Many allergic reactions to pollens, foods, antibiotics, and other agents result from sensitization (or antibody production) against specific antigens in these substances.

The A and B Antigens. Landsteiner identified two antigens in human red blood cells and designated them A and B. It has been found that a person can have one antigen or the other, both antigens, or neither of them. These four conditions make possible the four blood types.

Strange to say, however, blood plasma always contains all the antibodies that would not clump its possessor's own cells. For instance, a person having the A antigen could not also have the anti-A antibodies, for they would clump his own cells, but he could and does carry the anti-B antibodies. This situation is strange be-

cause the anti-B antibodies will be present even though the person has never contacted the B antigen. Likewise, anyone having the B antigen will have anti-A. All other antibodies seem to be present only because they have been stimulated into production through contact with antigens. Such antibodies resulting from the contact with the antigens are known as **immune antibodies**, while those that react with the A and B antigen are called **naturally occurring antibodies.** The relationship between the blood types and their antigens and antibodies is shown below.

Blood Type	Antigens Present in Red Blood Cells	Antibodies Present in Serum	Approximate Frequency in U.S. (percentage)
O	neither	anti-A and anti-B	47
A	A	anti-B	40
B	B	anti-A	10
AB	AB	neither	3

To type blood a drop of blood is mixed with a drop of serum from a person who is type B. This serum will contain anti-A, and if the red cells clump, it is evident that the blood being tested contains antigen A. Another drop of blood is mixed with serum from a type A person. This serum will contain anti-B; thus red cell clumping in this mixture indicates the presence of the B antigen. The four blood types can be identified by these two tests. The reaction of each of the four types of blood with these sera is shown in the following table.

Blood Type	Reaction with Anti-A (from Type B Blood)	Reaction with Anti-B (from Type A Blood)
O	no agglutination	no agglutination
A	agglutination	no agglutination
B	no agglutination	agglutination
AB	agglutination	agglutination

In blood transfusions it is customary to administer only blood of the same type as the recipient, but in an emergency it is possible
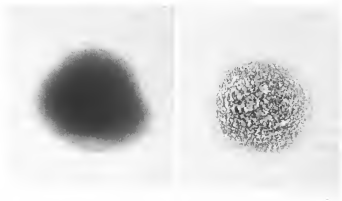
Fig. 11-1. Agglutination of human red blood cells is shown at right compared to a smooth mixture at left. Blood from a person who is type A is mixed with serum from a person who is type A at left. At right the serum is from a person who is type B; it contains anti-A antibodies.

to use certain other types. The important thing to keep in mind is that blood cells should never be introduced into a person who has antibodies that will clump them. It is possible to introduce blood containing antibodies against the antigens in the cells of the recipient because these antibodies will be quickly diluted by the plasma of the recipient and will drop below the titer, or concentration, necessary to cause clumping. For instance, type A blood should never be given to a person with type O because the anti-A type O blood would quickly clump the donor cells and cause death of the recipient as the large clumps of cells clog the small blood vessels. Type O blood, however, could be given to a type A person because the anti-A in the donor serum would be diluted below the titer needed to cause clumping by the large amount of plasma in the recipient. For this reason it is possible to give plasma transfusions without typing. It is the cells, not the plasma, being introduced that must be considered.

Inheritance of the ABO Groups. Multiple alleles at an autosomal locus account for the inheritance of ABO groups. Three basic alleles are responsible. One gene produces the A antigen, one the B antigen, and the third produces neither antigen. These genes are sometimes given the symbols, I^A, I^B, and I^O, the I standing for the term **isohemagglutinin.** Because the symbol I is used for another

blood group system, however, it is preferable to use another designation for the ABO groups, one that has the advantage of indicating dominance relationships:

a—neither antigen A—A antigen A^B—B antigen

As the letters indicate, a is recessive to the other two alleles, while A^B and A are codominant. Type AB blood results when a person is heterozygous for these two genes. There are six possible genotypes and four possible phenotypes. Later it was found that two different subtypes of anti-A sera could be isolated, and these could be used to identify two varieties of the A antigen. These varieties became known as A_1 and A_2 with corresponding gene symbols, and the variety of phenotypes was extended from four to six. There are two varieties of type A and two of type AB blood. These subtypes have no significance in blood transfusions but are of value in cases of disputed parentage.

The H Substance. A man in Bombay, India, was found to have blood that was not agglutinated with either anti-A or anti-B sera, yet his parents were types A and AB. Such parents seemingly could not have a child with type O. This man must have received the gene for A or B from the AB parent. Then it was found that he failed to produce a necessary precursor of the A and B antigens. The precursor was called substance H, and the gene producing it was designated H. This man was homozygous for the recessive allele h, so he had no A or B antigens even though he had the gene for one or both of these antigens. This condition has been called the **Bombay phenotype**, and other individuals who express it have since been discovered. The recessive gene h is epistatic to the genes for A or B antigens.

It was then discovered that the H substance could be identified by mixing the blood to be tested with serum from the blood of an eel or an extract of a plant, *Ulex europeus*. Persons having type O blood have an abundance of the H substance because none of it is converted into A or B antigens. As a result the blood cells are agglutinated in the test. Persons heterozygous for A or B will also have some H substance because all of it was not used in making the A or B antigens. The eel serum will agglutinate their red blood cells. Those homozygous for A or B and those who are AB will use practically all of the H substance in antigen production, so their blood will not agglutinate. Hence it is possible to identify

heterozygotes by mixing blood with eel serum or the plant extract.

Detection of H substance has legal implications. Suppose a woman with type O who has a baby also of type O demands child support from a man who is type A. This man could be the father if he were heterozygous but not if he were homozygous. A test for the H substance in the baby's blood cells would give the answer.

The Secretor Trait. Still another pair of alleles is involved in the characteristics of the ABO blood groups. Some persons who have A or B antigens in the red blood cells also have these antigens in their body secretions, such as saliva, gastric juice, and the secretions of the nose and eyes. Such people are known as secretors. Persons having A or B antigens in the blood cells, but not in their secretions, are nonsecretors. Those who carry the dominant gene *Se,* along with *H,* produce the H substance in the body secretions. If they also have genes *A* or *A^B,* the H substance is converted into the A or B antigens. Nonsecretors do not produce the H substance in their secretions and so have no A or B antigens in these secretions. About 70% of the people of the United States are secretors.

Identifying secretors is relatively simple. If blood-typing shows a person to be type A, a drop of his saliva is mixed with a drop of anti-A serum. The antigens and antibodies combine, but since there are no cells in the saliva, there is no clumping. The antibodies are bound to the antigen, however, and are not free to combine with additional antigens. A drop of the person's blood is then added to the mixture. If he is a secretor there will be no reaction, but if he is not a secretor the red cells will be agglutinated by the free anti-A. Type B persons can be tested with anti-B in the same way, and type AB can be tested with either antiserum. Type O can be tested by using the H-clumping factor from eel serum. The test is so sensitive that a bit of dried saliva left on an envelope after sealing can be used to determine if the person is a secretor; if he is, his blood type can also be determined. Such information can be of value in criminal cases.

THE RH ANTIGENS

After the discovery of the ABO blood groups transfusions began to be widely used in medical practice, but in some cases agglutination occurred even though the blood types were matched. In 1940

Landsteiner and Wiener found that a factor in the red blood cells of rhesus monkeys was also present in some human red blood cells and caused agglutination in those cases. They designated this antigen the Rh factor. Persons possessing it were known as Rh positive and those who did not were known as Rh negative. A dominant gene appeared to code the Rh factor. About 85% of Americans were found to be Rh positive, while the remaining 15% were Rh negative.

Rh Antibodies and Blood Transfusions. The Rh factor was found to differ from the AB antigens in that there were no naturally occurring antibodies for it in the serum of Rh negative persons. It is possible, however, for Rh negative individuals to develop such antibodies if they receive a transfusion of Rh positive cells. A second transfusion of positive blood after such sensitization

Negative mother
Negative child
Baby normal

Same mother
Positive child
Baby normal
Mother sensitized

Same mother
Second positive child
Baby born with
erythroblastosis
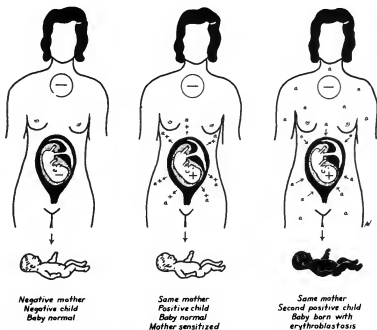
Fig. 11-2. Rh-induced erythroblastosis. When an Rh negative woman bears a positive child she may develop antibodies against the Rh factor. When she has a second positive child these antibodies may enter the fetus and destroy blood cells. (From Winchester, Biology, Van Nostrand.)

would result in agglutination of the transfused cells and death of the recipient, even though the blood types matched. Now the Rh factor, as well as the blood type, is determined before transfusions. Rh positive blood is not given to Rh negative persons, even though the first transfusion would cause no harm, because it would sensitize the recipient. This practice restricts the number of potential donors. For instance, a type O, Rh negative person could only take blood from another type O, Rh negative and this would be only about 7% of the population in the United States ($0.47 \times 0.15 = 0.0705$).

Maternal-Fetal Incompatibility. Another medical mystery was solved as a result of the discovery of the Rh factor. For many years babies had been born with **erythroblastosis fetalis,** or **hemolytic disease** of infants. Such babies were anemic and jaundiced and had many nucleated red blood cells, which do not carry oxygen as well as normal, nonnucleated red blood cells. Some babies with this disease died before birth. Rh factor determination showed that the mothers of such children were Rh negative and the afflicted babies were Rh positive. This trouble never seemed to occur at a mother's first delivery. During birth, when the placenta is separating from the wall of the uterus, there is considerable bleeding and quite a few fetal red blood cells enter the mother's circulation. If the baby is positive and the mother is negative, she might be sensitized by the invasion of these foreign antigens. When she bears a second positive child, some anti-Rh from her plasma will penetrate the placenta and react with the red cells of the fetus. The titer of these antibodies may be sufficient to destroy many red blood cells. To compensate, the bone marrow pours out immature, nucleated red blood cells. The result is a severe anemia and jaundice as the small blood vessels in the liver become clogged with broken cells.

Prevention of Sensitization. Recently a method was found to prevent Rh negative women from being sensitized when they bear their first Rh positive baby. The mother can be injected with anti-Rh immediately after the birth of the child. These antibodies react with and neutralize the antigens in the fetal red blood cells, which may have entered her circulation. Thus she develops no anti-Rh herself and can bear as many Rh positive babies as she wishes. The injected antibodies disappear from her blood over a period of six to eight weeks in the normal turnover of her blood.

The antibodies are obtained by injecting volunteer Rh negative men or postmenopausal women with the Rh antigens that sensitize them. Then a pint of blood is removed and the gamma globulin fraction is extracted from the serum; the rest of the blood can then be given back to the donor. This gamma globulin (called *Rhogam* by one producer) contains anti-Rh. Such injections are of no value for women who have been sensitized from previous births. They already have anti-Rh in their blood and continue to produce it.

Complexities of the Rh Factor. Continuing investigation showed that the Rh factor is more complex than was first believed. It was found that three antigens, not just one, may be present. A. S. Wiener proposed the theory that there are eight alleles at the Rh locus and that four of these could produce more than one antigen (see table 11–1). R. A. Fisher proposed an alternate theory based on pseudoalleles. He maintained that there are three loci lying very close together on the chromosome that account for the different antigens. According to this theory, there are three genes for the Rh complex on each of the two homologous chromo-

TABLE 11–1
GENE SYMBOLS AND FREQUENCIES OF THE RH FACTOR

Genotypes		Approximate Frequency in Population (percentage)
Wiener's Notation	Fisher's Notation	
r/r (neg.)	cde/cde	15.00
R_1/r	CDe/cde	35.00
R_1/R_1	CDe/CDe	20.00
R_2/r	cDE/cde	12.00
R_2/R_2	cDE/cDE	2.00
R_1/R_2	cDE/CDe	13.00
R_0/r	cDe/cde	2.00
R'/r	Cde/cde	0.75
R''/r	cdE/cde	0.85
R_0/R_0	cDe/cDe	rare
R'/R'	Cde/Cde	rare
R_x/r	CDE/cde	rare
R_y/r	CdE/cde	rare

somes. The positive genes are designated as C, D, and E, and their negative alleles are c, d, and e. Thus a man carrying all three dominant genes would have the three positive antigens. He would be Rh positive if he carried even one of the three dominant genes, while an Rh negative person would be homozygous for all three recessive alleles. Three antisera are necessary to detect which of the antigens are present. Often these sera are combined into one mixture, anti-CDE. If a person carried one or more of the antigens, his blood would be agglutinated by this mixture.

Rh^D is the most common positive antigen, being present in about 98% of persons who are Rh positive. The D antigen is also the most highly antigenic. A person who is Rh^C positive can be sensitized by a transfusion of Rh^D positive blood and may die after a second such transfusion. Also, a positive C mother can be sensitized by a positive D fetus. Hence those who lack the D antigen are usually treated as if they were negative to avoid any complications. Table 11–1 shows the genes involved according to both the Wiener and the Fisher theories, the antigens present, and the frequencies of the different combinations. You will note that antigen E is very rare. It is also very weakly antigenic, so it seems to cause no difficulties.

A further complication was noted when homozygous CC persons occasionally develop some sensitivity to blood from one who is homozygous cc. It seems as if there is some precursor, as in the ABO groups, and this may cause sensitization in rare cases when the recipient does not have at least one c. This idea was supported by the discovery of a few people who are Rh null. Their blood does not react to any of the antisera.

OTHER RED BLOOD CELL ANTIGENS

Quite a number of other red blood cell antigens have been discovered, and these have added greatly to the possible varieties of human blood.

The MNS Antigens. In 1927 it occurred to Landsteiner and Levine that there might be some blood antigens to which the human body does not respond by antibody production, but to which other animals would respond. To test this possibility, they injected human red blood cells into rabbits. They found that the

rabbits did indeed produce immune sera that would react with some human blood samples but not with others. The results from sixty-four families indicated that two antigens, which they called M and N, were produced by allelic genes not related to the ABO locus. The genes were codominant, so people could be classified into three groups: M, N, and MN. There were no gene equivalents of a in the ABO series. In honor of Landsteiner we now use the symbols L^M and L^N for the two alleles. Since people do not produce antibodies against the MN antigens, these antigens have no clinical significance but are valuable in extending the number of blood traits that can be included in medicolegal and population studies.

About 20 years after the M and N blood antigens were discovered the Ss groups were identified and found to belong to the MN system. Two genes, S and s, at another locus were responsible. S apparently produces its antigen from the same precursor substance used in the production of M and N. The recessive allele does not produce the S antigen. People can thus be identified according to six groups: MS, Ms, MS, Ns, MNS, MNs. Since the discovery of the MNS antigens, about a dozen other genes have been found to involve the same precursor and thus belong to the same system.

Discovery of Other Antigens. Other antigens have been discovered when people became sensitized during transfusions or childbirth and no known factors seemed to be responsible. For instance, a Mr. And received a blood transfusion and showed some reaction even though all the known blood antigens matched. He lacked an antigen that was present in the donor blood and had been mildly sensitized by previous transfusions. The antigen he lacked was designated the **Xg antigen** and was found to be sex-linked. Since there are only two alleles, people can be classified as Xg positive or Xg negative.

Another antigen was discovered when a Mrs. Kell bore a child with mild symptoms of erythroblastosis even though she was Rh positive. It was found that her husband's blood contained an antigen that she did not have. Her child was Kell positive and she had been mildly sensitized by a previous birth of such a child.

A **Lewis antigen** was discovered when a Mrs. Lewis had similar trouble. Other antigens appeared shortly thereafter, and some of them are listed in table 11–2.

In addition to the great variety of antigens on the cell membrane

TABLE 11–2
ANTIGENS IN VARIOUS BLOOD GROUP SYSTEMS

System	Antigens Detected	System	Antigens Detected
ABO	A, B, H	Lutheran	Lu^a, Lu^b
MNSs	M, M^g, M$_1$, N, N$_2$, S, s,	Kell	K, k, Kp^a, Kp^b,
	U, Mi^a, Vw, Mu, Hu, He,		Js^a, Js^b, K^o.
	Vr, Mt^a, Ri^a, St^a	Duffy	Fy^a, Fy^b, Fy^x
Rh	See table 11–1	Diego	Di^a, Di^b
Xg	Xg^a	Auberger	Au^a
Lewis	Le^a, Le^b	P	P$_1$, P$_2$, P^k
Dombrock	Do^a	I	I

of red blood cells, other parts of the blood also show considerable genetic variation. The hemoglobin within the red blood cells, for instance, shows many inherited varieties. The other blood cells and the plasma proteins have also come in for their share of genetic investigation, and many varieties of these have been uncovered. It should now be apparent why we said at the beginning of this chapter that blood is a very distinctive human characteristic.

PROBLEMS

1. A man has type A blood and his wife has type B blood. When she bears a child who is type O, he accuses her of infidelity because he feels that he could not be the father of such a child. On the basis of this information alone, is there any justification for his suspicions?

2. Further tests are made to try to settle the question mentioned in problem 1. He proves to be Rh^D positive, while both mother and child are Rh negative. His blood showed no agglutination when mixed with anti-H, but that of both his wife and child did agglutinate when mixed with anti-H. Do these tests have any bearing on the case? Explain.

3. A man receives an extortion letter and the police analyze the dried saliva left when the gum was licked to seal the envelope. They find that the saliva contains the B antigen but not the H

antigen. What genes do you know were possessed by the writer of the letter?

4. A suspect is found in the case described in problem 3 and his blood reacts with anti-B and anti-H. He also proves to be a secretor. He denies any involvement. What are the mathematical odds that he was telling the truth?

5. An Rh positive man has the Fisher genotype *CDe/cde*, while his wife has *cDe/cDe*. Could they have a negative child? Explain.

6. A baby is kidnapped. Several years later a child is found who might be the kidnapped child. Blood tests of the parents and the child are given below. Could this be their lost child? If so, what are the mathematical odds that this is the wrong child who just happened to have these blood characteristics by coincidence?

	Anti-A	Anti-B	Anti-H	Anti-M	Anti-N	Anti-D
Mother	+	—	+	+	—	+
Father	+	—	+	+	—	+
Child	—	—	+	+	+	—

7. A woman learns that she had Rh-induced erythroblastosis when she was born and is worried that she may have a child who would also be so afflicted. What could you tell her about her chances for such an event?

8. What effect would the extensive use of Rhogam to prevent sensitization of negative women have on the frequencies of the genes for the Rh factor in future generations?

12. GENE LINKAGE

Early in his work, Mendel discovered the principle of independent assortment. When he crossed green wrinkled peas with yellow round peas he obtained the recombination of green round and yellow wrinkled just as freely as the parental combinations. When chromosomes were discovered as the carriers of the genes, it was easy to see why this condition occurred. In meiosis there exists a random arrangement of the chromosomes during the metaphase, and genes lying on different chromosome pairs will be assorted independently of their association in the parents.

Had Mendel selected two characteristics dependent on two genes that occupied the same chromosome he would not have obtained independent assortment. Such genes tend to remain together during meiosis and are said to be linked genes. Subsequent studies of the linkage phenomenon have led to valuable discoveries.

DISCOVERY OF LINKAGE

In 1903 Sutton, at Columbia University, predicted linkage by reasoning that, since the number of genes must far exceed the number of chromosomes, there would be many genes on each chromosome and these would not be expected to show free recombination.

First Demonstration of Linkage. Only three years after Sutton's prediction the first case of linkage was reported by the English geneticists Bateson and Punnett in their study of the sweet pea. In their experiments they crossed a plant that bore red flowers and spherical pollen grains with yellow flowers and cylindrical pollen grains. A testcross of the F_1 was made and, to their surprise, yielded a ratio that was approximately 7:7:1:1 instead of the expected 1:1:1:1. The two smaller classes repre-

sented the recombinations. This led the geneticists to suspect that the two genes involved were linked, and further study showed that indeed this was the case. The fact that there occurred any re-combinations at all, however, showed that there must be some mechanism for the separation of genes that lie on the same chromosome. We shall soon explain how this occurs.

Determining Chromosome Number by Linkage Groups. Further genetic crosses with the sweet pea showed that there were seven groups of linked genes; cytological studies revealed there were seven pairs of chromosomes. In *Drosophila* four linkage groups of genes were found corresponding to the four pairs of chromosomes that were demonstrated through studies of the cells. Thus it became evident that the number of chromosomes of an organism can be determined by genetic crosses provided a sufficient number of inherited characteristics can be found to ensure that genes from all chromosomes are represented. In actual practice both genetic crosses and cytological studies are carried out where possible.

CROSSING-OVER BETWEEN LINKED GENES

The work of Bateson and Punnett indicated that there is some method by which genes that lie on the same chromosome recombine. This process is known as crossing-over and involves the actual breakage and reattachment of chromatids when they are paired during the prophase of the first division of meiosis.

Mechanism of Crossing-Over. Cytological studies have yielded us a clue as to the mechanism of crossing-over. You will recall that during the early prophase of meiosis the chromosomes pair and each divides so that there are four chromatids (tetrads) in close association. At this time there may be simultaneous breakage and reattachment between homologous chromatids; this process creates a new association of genes. The latter condition is illustrated in figure 12–1 better than words can describe. As the chromosomes go into the latter part of the prophase and separate slightly from one another, crosses can be seen between chromatids of homologous chromosomes. These crosses, known as *chiasmata* (sing. *chiasma*), are shown clearly in the photograph in figure 12–2. It is generally agreed that the chiasmata represent regions where crossing-over has taken place, but there is some evidence
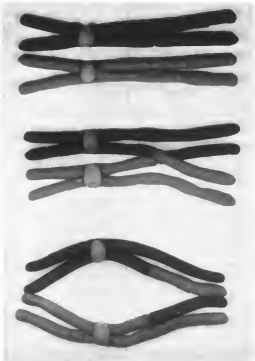
Fig. 12–1. The mechanism of crossing-over. Pieces of chromatids from synapsed chromosomes cross over with a simultaneous breakage and union to form new linkage groups.

that this may not be true for every chiasma. In the male *Drosophila,* for example, crossing-over does not take place under normal circumstances, yet some chiasma formation can be observed in the primary spermatocytes.

Variation in Amount of Crossing-Over. The amount of crossing-over may vary greatly and is correlated with the distance between the genes involved. If two genes lie close together, crossing-over might occur in only a fraction of 1% of the gametes produced. On the other hand, if the genes lie at opposite ends of a rather long chromosome, we would expect a high percentage of crossing-over. This condition can be illustrated by two cases of crossing-over in the domestic fowl.

A dominant gene F causes the feathers to be frizzled—they are brittle and curly and break off easily. Another dominant gene I inhibits the formation of color, causing the feathers to be white. Hutt crossed colored frizzled females with white normal leghorn males and testcrossed the F_1 with the following results:

P₁   *iF/iF* (colored frizzled) × *If/If* (white normal)
F₁   all *iF/If* (white frizzled)
     testcrossed with *if/if* (colored normal)

Results: *iF/If*   colored frizzled   63⎫
         If/if   white normal   63⎬ parental types 80.3%
         IF/if   white frizzled   18⎫
         if/if   colored normal   13⎬ recombinations 19.7%
                   Total   157

The fact that 19.7% of the offspring are recombinations gives proof that the two genes involved lie a considerable distance apart on the chromosome.

When two other linked genes were investigated, Taylor obtained very different results. He combined the creeper characteristic *Cr*, which causes the legs to be short and the chicken to creep about, and a comb characteristic *R*, which produces a rose comb while the recessive allele *r* produces the single comb. Since the gene for the creeper is lethal when homozygous, he began with heterozygous creepers and selected the creepers from the F₁ for the testcross.

P₁   *R cr/R cr* (rose normal) × *r Cr/r cr* (single creeper)
From offspring selected: *R cr/r Cr* (rose creeper)
Testcrossed with: *r cr/r cr* (single normal)

Fig. 12-2. Crossing-over in grasshopper chromosomes. This highly magnified photograph of a synapsed pair of chromosomes in a spermatocyte shows the chromatids from one pair crossing over with another. Four chiasmata, points of crossing-over, can be seen here.

Results: $R\ cr/r\ cr$ rose normal   1069 } parental types 99.5%
$r\ Cr/r\ cr$ single creeper   1104 }
$R\ Cr/r\ cr$ rose creeper   6 } recombinations 0.5%
$r\ cr/r\ cr$ single normal   4 }
                    Total $\overline{2183}$

The small percentage of recombinations seems to indicate that the two genes must lie very close together on the chromosome; thus the chance of their being separated by a crossover is very slight.

GENETIC APPLICATIONS OF CROSSOVER DATA

Through the use of the results of the crosses of linked genes we have been able to learn much about the gene arrangement on the chromosome.

Chromosome Distances as Determined by Crossing-Over. Since the amount of crossing-over is somewhat proportional to the distance between genes on the chromosomes, we can use the percentage of crossing-over as an indication of units of distance. One percent of crossing-over is taken to indicate one unit of distance. Using the results of the cross involving feather characteristics in the domestic fowl, we can say that the gene locus that determines color or lack of color lies 19.7 units from the gene locus that determines the frizzled or normal condition of the feathers. Likewise, the gene locus for the comb characteristics lies 0.5 unit from the gene locus for the creeper or normal leg condition.

Do these unit distances as determined by crossing-over correspond to the actual linear distances on the chromosome? We would expect them to be the same if crossing-over occurs with equal facility in all regions of the chromosome. Cytological studies reveal that there is some variation. For example, in *Drosophila* we find that there is less crossing-over in proportion to length near the centromeres and near the ends of the V-shaped chromosomes than there is in the region near the middle of each arm. Thus we would conclude that it is easier for the chromatids to cross in some regions of the chromosomes than in others.

The Effect of Double Crossing-Over. Early *Drosophila* studies on crossover percentages between two linked genes revealed that the value obtained was often less than the sum of crossover values of genes lying in between. For example, black body (*b*)

and vestigial wings (vg) are mutant genes that show linkage with a crossover of about 17% when only these two genes are used in the test. There is another mutant gene, cinnabar eye color (cn) which lies in between black and vestigial. Crossovers between black and cinnabar are about 9.0% and crossovers between cinnabar and vestigial are about 9.5%. The sum of the crossovers should be the distance between black and vestigial. However, this sum is 18.5 as contrasted with 17.0% obtained in crosses involving only black and vestigial. Why is there disparity in the results?

The answer may be found in double crossovers. In the black vestigial test a double crossover would restore the original order of genes and there would be no evidence of a crossover even though there had actually been two. Because of the disparity it is customary to use three genes (the *three-point cross*) for studies when the genes lie more than ten units apart. In some cases four, five, or more genes may be used. An example of the three-point cross is given below.

Black cinnabar vestigial flies were crossed to the wild type, and the heterozygous female offspring were testcrossed with black cinnabar vestigial males. (Only females are used from the F_1 because there is practically no crossing-over in the male *Drosophila.*) The results follow:

b^+ cn^+ vg^+ (wild type)	332	parental types 81.5%
b cn vg	326	
b cn^+ vg^+	35	crossovers between b and cn
b^+ cn vg	31	
b cn vg^+	36	crossovers between cn and vg
b^+ cn^+ vg	34	
b^+ cn vg^+	4	double crossovers 0.86%
b cn^+ vg	2	
Total	800	

Crossovers between b and cn (includes doubles)   76 or   9.5%
Crossovers between cn and vg (includes doubles)   72 or   9.0%
Total between b and vg (doubles counted twice)   148 or 18.5%
Total between b and vg (doubles not counted)   136 or 17.0%

From these results we can see that had we made the cross without including the mutant cinnabar we would have obtained a crossover distance of 17 units rather than 18.5 units because of the difficulty in detecting the double crossovers.

Interference and Coincidence. When two genes are in close proximity, we do not obtain any double crossovers between them. In other words, crossing-over at one point seems to inhibit crossing-over within a certain distance on either side. This inhibiting effect is known as *interference.* In *Drosophila,* interference prevents a second cross for a distance of about ten units and then gradually diminishes as the genes become farther apart. The degree of interference varies in different parts of the chromosome, in different chromosomes of the same species, and in the chromosomes of different species.

We can express the degree of interference in terms of *coincidence;* thus interference is calculated by dividing the number of the obtained double crossovers by the expected frequency of doubles. We can determine the expected percentage of doubles by multiplying the percentage of crosses at the two regions involved. Using the *Drosophila* cross as an example, we obtain the following results:

Percent crosses between b and cn	9.00%
Percent crosses between cn and vg	9.50%
Expected doubles if there is no interference	
(0.09×0.095)	0.86%
Expected number of doubles (0.86% of 800)	7.00
Obtained number of doubles	6.00
Coincidence of interference 6/7	0.86

We see that coincidence varies inversely as the degree of interference. The interference could extend from zero, which would be complete inhibition, to one, which would yield no interference at all.

CHROMOSOME MAPPING

In organisms where a considerable number of variable inherited characteristics are known and crossover studies are possible on a large scale, maps of the chromosomes can be made showing the relationships of the different genes to one another. Such maps have been worked out for *Drosophila,* for corn, for mice, for some of the molds and bacteria, and to a limited extent for man.

Mapping of X-linked Genes in *Drosophila.* The methods used in chromosome mapping can be illustrated by a case involving

the X chromosome of *Drosophila*. There exists a recessive gene for
yellow body color that has been given the position of 0.0 on the
chromosome because no other genes have been found on the other
side of it and cytological studies show that the gene is at, or very
near, one end of the chromosome. Suppose, then, that we have
two other X-linked genes that we would like to place properly on
the map. X-linked genes are preferable for use in experimental
crossover studies because the researcher can allow the F_1 to breed
inter se and study the results in the F_2 females. The genes we wish
to locate are miniature wings *m* and forked bristles *f*. The results
of the crossover are not arranged in any particular sequence. They
are listed at the bottom of this page as one might have tabulated
them from the actual fly counts without knowing the arrangement
of the genes on the chromosome.

Before proceeding further, we must determine the proper se-
quence. Since the *y* is at a location of 0.0, we know that it will be
to the "left" of the other two, but which gene comes in the middle?
Is the sequence *y m f* or *y f m*? The problem is most readily
determined by examining the double crossovers. A double cross-
over will remove the middle gene from the other two genes and it
will stand alone in one of the double crossover classes. The genes
on either end will be together in the other double crossover class.
The double crossovers will be expected to be the two smallest
classes. When we examine the results of the crossing-over, we find
that number (2) and number (6) are evidently the double cross-
overs. Number (2) shows that miniature is in the middle class
since it stands alone in the new genes for body color and bristles.
Number (6) shows that *y* and *f* are on the ends.

P_1 *y m f*/*y*+ *m*+ *f*+ males × *y*+ *m*+ *f*+/*y*+ *m*+ *f*+ females

F_1 *y m f*/*y*+ *m*+ *f*+ females × *y*+ *m*+ *f*+/Y males (*inter se* cross)

Results F_2 females only:

	y+ *m*+ *f*+	26 } parental types 50%
	y m f	24
(1)	*y*+ *m f*	14
(2)	*y*+ *m f*+	2
(3)	*y*+ *m*+ *f*	8
(4)	*y m*+ *f*+	16 crossovers
(5)	*y m f*+	6
(6)	*y m*+ *f*	4
	Total	100

Having solved this problem, we now put the classes together in proper sequence and determine the crossover percentages.

Crossovers between y and m:
Add 1, 4, 2, and 6 = 36 or 36% of the total.
Crossovers between m and f:
Add 3, 5, 2, and 6 = 20 or 20% of the total.
Coincidence of interference:
6/7.2 = .83

Using the results of this cross we can tentatively place miniature 36 units to the "right" of yellow and forked 20 units to the "right" of miniature. The units can be placed on a chromosome map as follows:

y	m	f
0.0	36	56

If we wanted our results to be more reliable, we would have to include many more flies in our study and even consider the coincidence of interference in establishing the locations of these genes. Using such techniques, geneticists have established the extensive chromosome maps such as the one illustrated in table 12–1, which shows only a comparatively few of the genes that have been located on the *Drosophila* chromosomes.

Pseudoalleles. In the course of study of thousands of *Drosophila*, some very interesting cases of crossing-over have been found between genes that were apparently alleles. There are two genes which alter the shape and texture of the eye. They are known as Star (S) and asteroid (*ast*). For many years the genes were thought to be alleles since they seemed to occupy the same locus on the chromosome. Recently, however, it has been found that there is a crossover frequency of 0.02% between these two genes, or a frequency of only one in 5000. Since they are so close together and since they affect the eye in a similar way, it is thought that the two must have been true alleles at one time, but through some slight misalignment of chromatids in crossing-over two genes of the same kind were found on one chromosome. Mutation could have caused the variation of effects. A number of such genes have been discovered in such widely divergent organisms as corn, molds, and bacteria, as well as in *Drosophila*. You will recall also from the discussion in chapter 11 that one of the most widely

TABLE 12-1

LOCATION OF SOME BETTER-KNOWN GENES OF *Drosophila melanogaster* AS DETERMINED BY CHROMOSOME MAPPING

X Chromosome I		Chromosome II		Chromosome III		Chromosome IV	
0.0 *y*	yellow body	0.0 *net*	net veins	0.0 *ru*	roughoid eyes	0.0 *sv*	shaven bristles
0.0 *ac*	scute bristles	1.3 *S*	Star eyes	0.2 *ve*	veinlet wing	0.0 *ci*	cubitus interruptus
0.6 *br*	broad wing	11.0 *ed*	echinoid eyes	19.2 *jv*	javelin bristles		venation
0.8 *pn*	prune eyes	13.0 *dp*	dumpy wing	26.0 *se*	sepia eye	0.0 *gvl*	grooveless scutellum
1.5 *w*	white eyes	16.5 *cl*	clot eyes	26.5 *h*	hairy body	0.2 *ey*	eyeless
3.0 *fa*	facet eyes	41.0 *J*	Jammed wing	41.4 *Gl*	Glued eye		
5.5 *ec*	echinus eyes	48.5 *b*	black body	43.2 *th*	thread arista		
6.9 *bi*	bifid wings	51.0 *rd*	reduced bristles	44.0 *st*	scarlet eyes		
7.5 *rb*	ruby eyes	54.5 *pr*	purple eye	45.3 *cp*	clipped wing		
13.7 *cv*	cross-veinless wings	55.0 *lt*	light eye	46.0 *W*	Wrinkled wing		Y chromosome
		55.9 *tf*	tarsi fused	47.0 *in*	inturned bristles		
18.9 *cm*	carmine eyes	57.5 *cn*	cinnabar eye	48.0 *p*	pink eye		
20.0 *ct*	cut wing	67.0 *vg*	vestigial wings	48.7 *by*	blistery wing		
21.0 *sn*	singed bristles	72.0 *L*	Lobe eye	50.0 *cu*	curled wing		male fertility
27.7 *lz*	lozenge eyes	75.5 *c*	curved wing	58.2 *Sb*	Stubble bristles		long bristles
32.8 *ras*	raspberry eyes			58.5 *ss*	spineless bristles		male fertility
							(no locations worked out)

TABLE 12–1 (Cont'd)

X Chromosome I	Chromosome II	Chromosome III	Chromosome IV
33.0 v vermilion eyes	100.5 px plexus veins	59.0 Rf Roof wing	
36.1 m miniature wings	104.5 bw brown eyes	62.0 sr stripe thorax	
43.0 s sable body	107.0 sp speck wing	63.1 gl glass eye	
44.4 g garnet eyes		66.2 Dl Delta veins	
51.5 sd scalloped wings		69.5 H Hairless bristles	
56.7 f forked bristles		70.7 3 ebony body	
57.0 B Bar eyes		90.0 Pr Prickly bristles	
59.5 fu fused veins		91.1 ro rough eyes	
62.5 car carnation eyes		93.8 Bd Beaded wing	
66.0 bb bobbed bristles		100.7 ca claret eye	
		104.3 bv brevis bristles	

Data from Bridges and Brehme

accepted theories explaining the complexities of the Rh factor depends on pseudoallelism.

Position Effect. Pseudoalleles usually express what is known as a position effect of the genes—meaning that the same genes produce different phenotypes when they are in different positions. We can illustrate this with a pair of pseudoalleles affecting eye color in *Drosophila*. As we learned in chapter 10 the white eye series of multiple alleles is quite extensive. There is recent evidence that the genes for white and apricot might more properly be classified as pseudoalleles. When white-eyed males are crossed with apricot-eyed females, the female offspring have light-apricot eyes as would be expected from the heterozygous effect of alleles. The males have apricot eyes since these genes are on the X chromosome. In the F_2 the males are half apricot and half white as would be expected in a typical monohybrid sex-linked cross. E. B. Lewis, however, found that in a very large number of crosses a few red-eyed offspring appeared. He reasoned that these might be the result of crossovers and that the genes might more properly be represented as $apr^+ \; w^+$ (red), $apr \; w^+$ (apricot), and $apr^+ \; w$ (white).

According to Lewis's theory, the two genes do not behave in the same way as other dihybrids; the position effect comes into play. The wild-type genes must be on the same chromosome in order to assert their dominant effect over the other two. This is shown below.

Genotype	Phenotype
$apr^+ \; w^+/apr \; w$	wild-type red eye
$apr^+ \; w/apr \; w^+$	light apricot eye

Flies with these two genotypes have exactly the same gene combination, but they are in a different position with relation to one another and this alters their effect on the phenotype. (Details about the nature of gene structure and gene action are discussed in chapter 14.)

SIGNIFICANCE OF CROSSING-OVER IN SELECTION

The commercial plant and animal breeders appreciate crossing-over just as much as the theoretical geneticists. When the former

find some desirable characteristic linked to a characteristic which is undesirable, they need only to obtain hybrids and pick up crossovers in the second generation. Thus, the commercial breeder can select for the desirable characteristic and discard the undesirable one. The same is true of natural selection. Without crossing-over there would be selection on the basis of large blocks of genes. On any one chromosome there would almost certainly be some genes which would be beneficial and some detrimental to the welfare of the organism. The sum total effect of all of the genes on the chromosome would prove to be the deciding factor in selection. With crossing-over, however, it is possible for individual genes to be selected, since crossing-over provides recombinations with other genes. Also, the crossing-over permits selection on the basis of combination effects on different genes.

MAPPING GENES OF BACTERIA

Since bacteria are haploid, it is not possible to make crosses and determine gene distances by the amount of crossing-over. There is a way to map bacterial genes however, that is based on the time of transfer of genes during conjugation. For example, *E. coli* has a single circular chromosome and the Hfr donor injects a part of its chromosome into the F⁻ recipient. Because the number of genes transferred depends on the time the conjugants remain together, then time equals distance on the chromosome. Suppose an Hfr donor carries genes that can synthesize arginine, phosphatase, and tryptophan (arg^+, pho^+, and try^+). It conjugates with a recipient that cannot synthesize any of these substances and thus has genes arg^-, pho^-, and try^-. If the conjugants are broken apart mechanically in a blender after at least 5 minutes has elapsed, some recipient cells will have received the gene arg^+ and can synthesize arginine. If the conjugants were left together for at least 10.3 minutes, the recipient would be found to be able to synthesize both arginine and phosphatase, while 24 minutes are required for the recipient to receive all three genes and acquire the power to synthesize all three substances. If we allow one minute of time to represent one chromosome unit, we can now map the three genes as follows:

0	5	10.3		24	30
	arg^+	pho^+		try^+	F

The F represents the male-determining factor which may be transferred if the bacteria are together at least 30 minutes.

PROBLEMS

1. In the somatic cells of a male grasshopper there are 23 chromosomes. How many linkage groups of genes would you expect to find from genetic crosses? Explain how you derive your answer.

2. In the mouse the diploid chromosome number is 40. The gene for the waltzing characteristic is located on chromosome 10. Suppose you discover a new gene for belted body. What are the chances that it will be linked to waltzing, assuming that all chromosomes are the same length?

3. Suppose you cross mice having the belted body with mice expressing the waltzing trait. The offspring are all normal, showing that both genes are recessive. You testcross the offspring by crossing to belted-waltzing mice. The results are given below. Do you think the two genes are linked? Explain.

Belted body	54	Belted-waltzing	57
Normal	49	Waltzing	47

4. *Drosophila* with curled wings and striped thorax (*cu, s*) are crossed with the wild type. The F_1 females (all wild type) are testcrossed with males expressing the double recessive. From the results given below do you think the genes for these two traits are on the same chromosome? If your answer is yes, give the percent of crossing-over.

Wild type	359	Striped-normal wings	51
Curled-striped	345	Normal body-curled	45

5. The genes m (miniature wings) and f (forked bristles) are located at 36 and 56 respectively on the X chromosome of *Drosophila*. Carnation eye is due to another X-linked gene (*car*). From the following crossover results, where would you place the gene for carnation on the chromosome?

Crossovers between *m* and *car*   26%
Crossovers between *f* and *car*   6%

6. Three linked genes in corn produce the following characteristics: *gl*, glossy leaves; *v*, virescent (seedlings are first white, then yellow, and finally green); *va*, variable sterile (irregular distribution of chromosomes in meiosis). The results of the three-point cross are given below. Determine the proper sequence of these three genes on the chromosome and the distance between them.

gl^+ va^+ v^+ = 235	gl^+ *va* *v*	= 4
gl *va* *v* = 270	*gl* va^+ *v*	= 48
gl *va* v^+ = 62	*gl* va^+ v^+	= 7
gl^+ *va* v^+ = 40	gl^+ va^+ *v*	= 60

7. What is the coincidence of interference in problem 6?

8. If we assume that the pseudoallele theory of Fisher is correct for the Rh blood antigens, do the following gene combinations indicate a position effect? Explain your answer.

Genotype	Rh Factor	Rh Antigens Present
CDe/cde	positive	C and D
Cde/cDe	positive	C and D
cde/cde	negative	none

13. CHROMOSOME ABERRATIONS

The segregation of chromosomes during mitosis and meiosis is normally very orderly, but as in most biological processes, there are occasional deviations from the normal procedure. Aberrant chromosome arrangements fall into two broad categories: those involving portions of chromosomes, and those involving entire chromosomes.

ABERRATIONS INVOLVING PORTIONS OF CHROMOSOMES

We learned in chapter 12 that the synapsed chromosomes of the first meiosis often break and become reattached to their homologs in a mutual exchange of segments known as crossing-over. In some cases, however, the chromosome may break and a portion is lost or attached to a nonhomologous chromosome, with a consequent upset in the balance of genes. We say that the point of breakage is "sticky," although this does not imply a literal stickiness. The point of breakage, however, does have an affinity for attachment to other sticky points on chromosomes. When there is only one break in a cell, the broken pieces may become reattached in their original position and no aberration results. When two or more breaks occur, however, the pieces may become attached to other chromosomes. In some cases there may be breakage at two points on the same chromatid and reattachments can occur in such a way that there is a different arrangement of genes. Some of the types of aberrations that are due to chromosome breaks are described below.

Deletion or Deficiency. A chromosome is said to show a deletion or deficiency when it has lost a portion of its original material. A **terminal deletion** occurs when there is a simple break near

the end of a chromosome. As long as the cell does not undergo mitosis or meiosis, this causes no great harm. The genes can continue to function in both of the broken pieces. When a spindle figure is formed, however, the piece without a centromere will not line up and segregate. Hence it will be left behind as the chromosomes move to the poles. It will not be included in the nuclei that form and will soon disintegrate in the cytoplasm. Thus the cell will lack a block of genes. If the cell with the missing piece is diploid, alleles of the missing genes will be on the homologous chromosome, but the gene balance is upset. The group of genes homologous to the missing piece will be haploid but the rest of the genes will be diploid. (X-linked genes, of course, are excepted.) If a deletion is large, this alteration of gene balance can cause considerable phenotypic abnormality.

Very small deletions may not be lethal, but they can be detected genetically by the expression of recessive genes in heterozygous individuals. This was first discovered in a cross between waltzing mice and normal mice. A recessive autosomal gene affects the part of the inner ear that controls balance, and mice homozygous for this gene tend to fall from side to side when walking—remotely simulating waltzing. In a cross between a waltzing male and a homozygous normal female, one of the offspring showed the waltzing trait. Cytological examination of this mouse showed that a small portion of one chromosome was missing. Evidently, the missing piece must have contained the dominant normal allele of the gene for waltzing. Hence the recessive gene was expressed, even though only one allele was present.

An **intercalary deletion** is one in which a central portion of a chromosome is lost. It can occur when a loop is formed in a chromosome, the chromosome breaks, and the two ends fuse, leaving a small ring without a centromere. **Ring chromosome** formation can occur when the ring includes the centromere and both ends of the chromosome are lost. This case entails a double deletion, but the ring chromosome can continue to function and duplicate during mitosis and meiosis.

Isochromosome formation results from a horizontal division of the centromeres during mitosis. Normally, the centromere splits in a vertical plane so that each chromatid becomes an entire normal chromosome. If the centromere splits horizontally, however, and the chromosome has a nonterminal centromere, two

abnormal chromosomes result. Each will have duplicated portions of one end of the chromosome and will lack the other end. These are known as isochromosomes because they are duplicates of the same arm.

Duplication. A chromosome with two sets of homologous genes can also occur if a portion broken from one chromosome becomes attached to the homologous partner. An unequal crossing-over between homologous chromosomes can result in such duplication in one chromosome and a deletion in the other. Small duplications can account for pseudoalleles as discussed in chapter 10.

Inversion. Sometimes a chromosome breaks in two places and the center piece will become reattached to the two ends, but in reverse order. A loop on a chromosome could result in this type of aberration. No genes are lost, so there may be no phenotypic effect although the position of the genes in their new relationship may have some genetic significance. Inversions are usually detected in cytological studies of meiosis. Synapsis is usually a gene-for-gene pairing, but in portions of the chromosome where the genes do not match there will be a repulsion. Without synapsis in this inverted region, there can be no crossing-over. When geneticists want to keep a particular arrangement of genes intact on a chromosome
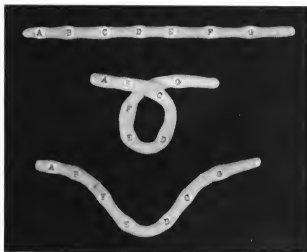
Fig. 13–1. Inversion, when the central portion of a chromosome is looped around on itself, breaks off and then reattaches, the genes in this portion are inverted with respect to their original order.
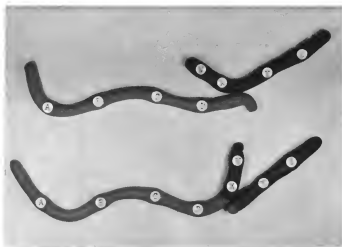
Fig. 13–2. Reciprocal translocation is illustrated here. The exchange is unequal.

with no crossing-over in heterozygous individuals, they often use stocks with an inversion of the chromosome involved.

Translocation. This type of aberration involves the exchange of portions by different chromosomes. A piece of one chromosome may become attached onto a nonhomologous chromosome. It appears as if this process is always accompanied by a simultaneous transfer of some of the chromosome in the reverse direction. This procedure, known as **reciprocal translocation,** is illustrated in figure 13–2. The exchanged portions may be quite unequal in size, but the end of a chromosome does not seem to be receptive to attachment unless it has also suffered a break, even though only a very small piece is broken off.

DROSOPHILA SALIVARY GLAND CHROMOSOMES

Geneticists for many years were handicapped in cytological studies because the chromosomes in the tissues they studied were too small to show details. Then it was discovered that the salivary glands of *Drosophila* revealed some of the largest chromosomes seen in any organisms. These giant chromosomes are of great value in studying chromosome aberrations and learning other facts about the relation of genes to chromosomes.

Fig. 13–3. The salivary gland of Drosophila. At left is an entire gland (enlarged) dissected from a mature larva. At right is a more highly enlarged section of the gland showing the very large size of the cells and their nuclei. It is even possible to see some of the chromosomes in some of these nuclei.

Appearance of Giant Chromosomes. The maggotlike larvae of *Drosophila* have a large pair of salivary glands, which are made of unusually large cells. These cells are laid down early in embryonic development and continue to enlarge, but no longer divide. When the glands are smeared on a slide and viewed under the microscope, chromosomes can be seen that are about a hundred times longer and much thicker than those seen in cells from other parts of the larva. Furthermore, the chromosomes can be seen in all salivary gland cells, while in other tissues chromosomes appear only in those cells that are in mitosis or meiosis. Also, the chromosome number seems unusual. Diploid cells from other parts of *Drosophila* have eight chromosomes, but those in the salivary glands have five long chromosome arms extending out from a central mass, the **chromocenter.** How can we account for all these differences?

First, the chromosomes are so long because they are uncoiled interphase chromosomes. They can be seen in all salivary gland cells because all these cells are in interphase. Second, these chromosomes are so thick because they have undergone repeated dupli-

cation, but without cell division. There may be a thousand or more individual strands in each chromosome, hence the name *polytene chromosomes*. Third, the presence of five arms can be explained by **somatic synapsis**, that is, each chromosome is paired with its homologous mate, something that usually occurs only during the first meiosis. We should therefore see four synapsed chromosomes, so why do we see five arms?

The chromosomes radiate out from the chromocenter, which represents the centromeres of the chromosomes together with the portion of each chromosome that contains few genes (the **heterochromatin**). The portions containing most of the genes, the **euchromatin**, make up the radiating arms. The X chromosome with its terminal centromere makes one arm of the five. If the larva is male this arm will be only half as thick as in female larvae because it will contain a single X, not a synapsed pair. The Y chromosome, which is almost devoid of genes, will mostly be enclosed in the chromocenter. The second and third chromosomes have median centromeres, so each has two long arms extending out from the chromocenter. This situation accounts for the five arms commonly seen. Close examination, however, will reveal a
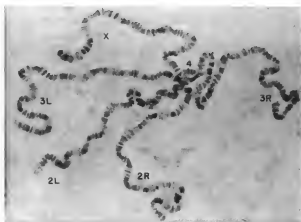
Fig. 13–4. The salivary gland chromosomes of Drosophila melanogaster. This is a photograph of a smear of the glands showing the five long arms coming out from the chromocenter. The origin of the arms is identified by the numbers and letters. (2 L is the left arm of the second chromosome, and so on.) (From B. P. Kaufmann, Carnegie Institute.)

small sixth arm extending out from the chromocenter—this is the very short fourth chromosome.

Banded Nature of the Chromosomes. When stained with dyes that have an affinity for DNA, the salivary chromosomes show an intricate pattern of alternating light and dark bands. Such bands can also be seen in the unstained chromosomes under the phase contrast microscope. This type of microscope achieves contrast from the differences in light refraction of different parts of the cell, indicating that there is a physical difference between the bands.

The bands of the salivary chromosomes are so distinctive that it is possible to identify even a small piece of a chromosome by its banding pattern. We can therefore identify translocations, inversions, and other aberrations. Small deletions can be located by the bulge in the normal chromosome synapsed with the one having the deletion. Individual genes can thus be associated with particular bands on the chromosomes.

Inversions and Translocations. Inversions show clearly in the salivary chromosomes because the inverted section will not synapse with the noninverted chromosome. A photograph of such an inversion is shown in figure 13–6. Translocations show up with equal clarity, and we can see parts of different chromosomes synapsed.
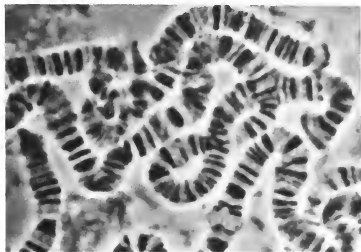
Fig. 13–5. Detail of giant chromosomes, showing their banded nature. A puffed region can be seen near the lower center.
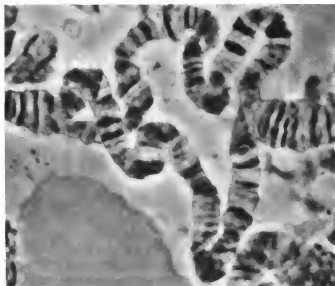
Fig. 13–6. An inversion shows clearly in this salivary chromosome. The two chromosomes do not synapse at the inverted region, but spread apart from one another.

ABERRATIONS INVOLVING ENTIRE CHROMOSOMES

Sometimes abnormal events during mitosis and meiosis can result in cells with abnormal chromosome numbers. There may be duplications or subtractions of only one or two chromosomes, or entire haploid sets may be involved. Aberrations involving less than a haploid set are known as aneuploids, while similar aberrations involving entire haploid sets of chromosomes may result in polyploids.

Aneuploids. In chapter 8 we learned that the sex chromosomes may fail to disjoin during meiosis, resulting in aneuploid sex chromosome numbers, which may be expressed as abnormalities of sex. Such nondisjunction can also occur in autosomes. Most often only a single chromosome is involved. When a cell receives one less than the normal diploid number, it is said to be **monosomic** for that chromosome. Cells having one extra chromosome are **trisomic** for the chromosome involved.

A. F. Blakeslee first showed some clear-cut examples of aneu-

ploidy in the Jimson weed, *Datura*. This plant has a normal diploid number of pairs of chromosomes, 12, but some trisomic plants were found with three chromosomes of one kind, and the other 11 pairs normal. Other monosomic plants were haploid with respect to one chromosome and diploid for the others. Some **polysomic** plants were found that had two or more extra chromosomes. Each aneuploid type resulted in a specific phenotype.

Aneuploids in animals are generally less viable than in plants, although some have been observed when the chromosome involved has been a small one. In *Drosophila* chromosome 4 is very small and both monosomy-4 and trisomy-4 have been found. Monosomics in humans do not survive, but several types of trisomics have been found, all of which cause great abnormalities. These are discussed later in this chapter.

Polyploids. Sometimes in mitosis the chromosomes duplicate but fail to separate and the cell goes back into interphase without dividing. The result is a **tetraploid** cell, one having four of each kind of chromosome. Later, normal mitosis takes place, producing a mass of tissue that contains tetraploid cells. If this occurs in the growing tip of a twig of a tree, the entire branch that grows out may be tetraploid. Such branches may produce superior varieties of fruit or other products. The branches can be propagated asexually by cuttings and graftings. Many of our commercial varieties of fruits are tetraploid and have been discovered accidentally on a diploid tree.

It is sometimes possible to propagate these plants from seed provided tetraploids are crossed. When both gametes are from tetraploids of the same species, the resulting plant is known as an **autotetraploid**. These plants are often of low fertility because, with four matching chromosomes in each cell, there can be some irregularity of distribution in meiosis. If pollen from one tetraploid species is used to fertilize ovules of a closely related, but different, species, the offspring are known as **allotetraploids** and have a high fertility because each chromosome has only one true homolog in the cell. When a tetraploid is crossed with a diploid of the same or different species, the offspring will be triploid and there can be no regular assortment of chromosomes in mitosis. Hence triploids are practically always sterile.

Polyploidy can also result from abnormal meiosis in which all the chromosomes are included in one diploid gamete. When this

gamete unites with a normal haploid gamete, a triploid zygote results. Only in the extremely unlikely event that a diploid gamete united with a similar diploid gamete would a tetraploid zygote be formed.

Animals having only tetraploid cells are generally not found. If an animal cell becomes tetraploid, that cell may multiply until there is an island of tetraploid tissue, but this tissue cannot grow into an entire animal. Triploids of *Drosophila* and other experimental animals have been found as a result of the formation of a diploid gamete which united with a haploid gamete, but these flies are sterile.

Induction of Polyploidy. In plant cultivation, it is sometimes desirable to artificially induce abnormal mitosis to obtain polyploids. The chemical, **colchicine**, is highly poisonous, but in minute quantities it has been used to treat human gout. When applied to cells in tissue culture it prevents the formation of the microtubules of protein which make up the spindle fibers. Hence, the late prophase chromosomes have no spindle figure upon which to become arranged, so mitosis stops at this point. The chromosomes are already duplicated, however, and they separate, but the cell does not divide and tetraploid cells result.

Plant geneticists have used this chemical extensively to induce polyploidy. When a very dilute quantity of it is applied to the growing tip of a plant the resultant new growth will be tetraploid. Most large flowers sold by florists have been produced by induced polyploidy. It is even possible to place colchicine on the growing tips of tetraploid plants and obtain octoploid tissue. Some scientists have even produced 16-ploid plants, but the beneficial effects of polyploidy seem to stop with tetraploidy.

Induced tetraploidy has made possible the hybridization of different species. As a rule, two different, closely related, species can be crossed to yield one generation of offspring, but these offspring are sterile, so it was not possible to produce a pure-breeding hybrid. If, however, the hybrid is treated with colchicine, the tetraploid tissue induced will produce viable gametes. Controlled pollination of two such tetraploids will produce tetraploid seed which will grow into a fully fertile hybrid variety. Using this technique, plant geneticists have produced a hybrid grain from wheat and rye. It is known as *Triticale* and seems to have some qualities superior to either parent. One of the first such hybridizations was made by

the Russian Karpechenko, who hybridized the radish and the cabbage. The plant proved to have leaves more like the radish and roots like the cabbage, however, so had no commercial value, but it did represent a great achievement which led to many practical applications.

Induced tetraploidy has also been used to produce seedless fruit. O. J. Eigsti found that by treating watermelon vine tips with colchicine he could get tetraploid melons. When these tetraploids were crossed back to the diploid variety, triploid zygotes were obtained, but they were so inviable that they would not grow into seed. Still the watermelons were formed, but they had no seeds. Such seedless watermelons are now being cultivated, although they have a long growing season and must be produced only in regions with such seasons.

Although colchicine cannot be used to produce tetraploid animals or fertile interspecific hybrids, it does have value in animal chromosome studies. Most human tissue cultures grown for chromosome studies are treated with this chemical several hours before they are placed on a microscope slide for observation. Many more of the treated cells show condensed chromosomes than do the un-
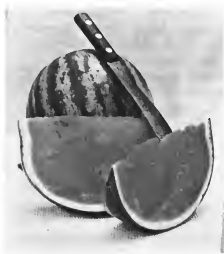
Fig. 13-7. A seedless watermelon. O. J. Eigsti, on a farm near Goshen, Indiana, found that he could produce seed which grow into seedless watermelons by crossing tetraploids with diploids. The result is triploid seed that grow into vines which produce melons having no seeds.

treated ones. When a treated cell enters prophase it cannot continue through mitosis because there is no spindle figure, so it holds in prophase for a time. Thus, there is a build-up of cells with late prophase chromosomes, facilitating chromosome studies. The colchicine also causes the chromosomes to become somewhat more compact, and the chance of seeing good mitotic figures without overlapping chromosomes is increased.

Colchicine can be injected into some experimental animals several hours before they are to be killed and cells removed for chromosome analysis. Bone marrow cells, for instance, will show many more cells with chromosomes in the condensed state after such injections. Studies of the intestinal cells of people who have taken colchicine extensively for gout may show islands of tetraploid tissue. Diploid eggs have been produced by rabbits who have been given injections of colchicine and these result in triploid offspring.

HUMAN CHROMOSOME ABERRATIONS

Not much was known about human chromosomes before 1956. They had been seen as early as 1870, but they were too small to study with the techniques available at that time. It was not until 1928 that an estimate was made of their number. T. H. Painter made very thin sections of human testes and saw some prophase cells with many tiny chromosomes crowded in the nuclei. He counted them as best he could and concluded that the diploid number was 48. In 1956, however, human cytogenetics really had its beginning. J. H. Tjio placed tissues from a number of aborted embryos on microscope slides, covered them with cover glasses, and squashed them very flat. When properly stained, many of the mitotic cells showed clear-cut and well-spread chromosomes. The diploid number proved to be 46. This technique was applied later to tissue culture cells taken from adults. Today most such studies are made from certain white blood cells, the lymphocytes. A few drops of blood can be treated so as to stimulate these cells to grow and divide. In order to better evaluate the chromosomes, a **karyotype** is usually made. From a photograph of a well-spread cell, the chromosomes are cut out individually, matched up in homologous pairs, and affixed to a sheet of paper according to length. Aberrations become readily apparent in such a karyotype.

In 1969 it was found that human chromosomes contained bands somewhat like those of *Drosophila* salivary gland chromosomes if stained and studied in a certain way. First, the chromosomes were stained with acridine dyes, such as quinacrine hydrochloride or quinicrine mustard. Then they were viewed under a special microscope using ultraviolet light. Certain parts of the chromosomes showed fluorescence while other parts remained dark. The parts that glowed brightly seemed to be the regions low in DNA because the Y chromosome is quite bright all over and we know that it has very few genes. The bands are distinctive for each chromosome, so it became possible to clearly identify each chromosome by its bands. Even pieces of chromosomes that had been translocated or otherwise rearranged could be recognized. About two years later it was found that a widely used blood stain, the Giemsa stain, would bring out the bands without the necessity of the ultraviolet microscope.

These improved techniques have shown that chromosome aberrations are a major cause of spontaneous abortions, neonatal deaths, and many kinds of abnormalities among the live born. We have already learned how the various characteristics can be influ-
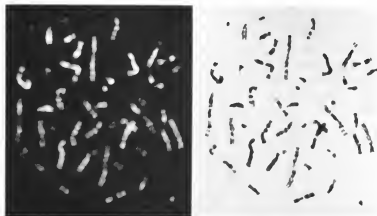
Fig. 13–8. Left, human chromosomes stained with quinacrine mustard and photographed under ultraviolet light. The banded nature is apparent. The Y chromosome can be identified to the right of upper center because it is very short and brightly fluorescent. Right, the same smear stained with Giemsa stain, photographed under ordinary light. The bands are obvious here, too.

enced by sex chromosome aberrations. Now let us consider the effect of aberrations on the autosomes.

Chronic Myelogenous Leukemia. This type of leukemia is characterized by a great increase in the number of white blood cells (leukocytes) that have granules in the cytoplasm. There is a corresponding reduction in red blood cells and a consequent anemia. Drugs that reduce the output of these granulocytes are now available, but this disease is still very serious. A karyotype of bone marrow from the sternum of a man in Philadelphia having this affliction showed that one of his chromosome 22s was shorter than the other. The shortened 22 is thus known as the Philadelphia chromosome (Ph¹). Other people having this type of leukemia were found to have similar deletions. The chromosome seems to have a weakness in a particular spot because all the breaks occur at about the same point. About 29% of the total chromosome is lost. The disease may appear at any age, but fetuses, babies, and young children seem particularly susceptible when exposed to excessive high-energy radiation or other mutagenic agents.

Cri du Chat Syndrome. Occasionally a baby is born having a cry that sounds like the mewing of a kitten in distress. The unusual cry is due to an improper closure of the vocal cords and is an indication that the baby has the *cri du chat* (cry of the cat) syndrome. These babies have a rounded face, a small cranium, and are severely retarded mentally. Karyotypes show that a part of the short arm of one of the chromosome 5s has been deleted.

Down's Syndrome (Mongolism). This is one of the most frequent of the abnormalities resulting from chromosome aberrations, afflicting about one in 700 newborns in the United States. This syndrome was also called "mongolism" because one of its characteristics is a downward fold of the upper eyelid, which roughly resembles the lid fold of members of the Mongolian races. Persons having this syndrome also have broad hands with stubby fingers, a wide rounded face, and a large tongue that may have furrowing. They are severely retarded. When it became possible to make human karyotypes in 1956, this was the first human chromosome aberration to be identified. Three chromosome 21s were found to be present.

Individuals with the trisomy-21 condition have a low viability and many die during their first year of life. They are very susceptible to respiratory infections and also may have heart defects. In the

Fig. 13–9. Girl with Down's syndrome. Although her genes are normal, she has received three chromosome 21s, resulting in mental retardation and other characteristics of the syndrome. Here she is being trained to do simple tasks within her capabilities.

past, few lived much beyond their twentieth birthdays, but today antibiotics and other treatments prolong their lives.

When a child is born with this syndrome, the parents are, of course, anxious to learn if their future children would also be likely to have the defect. Most cases arise as a result of nondisjunction of the chromosome 21s in the second meiosis of oogenesis. The chance of this nondisjunction occurring increases with the age of the mother and becomes over ten times greater in a woman past forty than in a woman in her twenties. (The reason for this was considered in chapter 4.) In general, the chance of having a second child with Down's syndrome is not appreciably greater if its presence in the first child was due to simple nondisjunction. In about 3.5% of the cases, however, a translocation is involved. In an otherwise normal parent one of the chromosome 21s may be translocated onto one of the other chromosomes. During meiosis the translocated 21 may go to the same pole as the single 21 to give a gamete with two 21s. Union with a normal

gamete would then give trisomy-21. In these cases the chance of a second child's having the syndrome would appear to be about one in three, since about one-third of the embryos that can survive to birth would be trisomy-21. Actual tabulations, however, show that only about 11% of the children of mothers with the translocation-21 have Down's syndrome. This may be the result of a higher rate of abortion of the fetuses with this syndrome; however, when a man has the translocation only about 2% of his children will have the syndrome. It appears that the abnormal chromosome complements do not have as good a chance to produce sperm as do the normal complements. Meiotic drive has been suggested as the answer. (Spermatocytes with aberrant chromosome arrangements do not have normal chromosome movement as readily as spermatocytes with normal chromosomes.) As a result fewer of the aberrant chromosomes are included in the viable sperm produced. A few cases have been found where a carrier parent had the two 21s attached to one another. All live-born children of such a parent would have the syndrome because only the sperm with the two attached 21s would give a viable fetus. Any parents who have had one child with Down's syndrome should certainly not consider another pregnancy until both parents

Fig. 13–10. Baby with Edward's syndrome, caused by three chromosome 18s. Note the peculiar shape of the ear, the receding chin, the extended back of the head, and the position of the fingers.

have had a karyotype to determine if either of them has a translocation.

Edward's Syndrome. This syndrome is caused by trisomy-18. A baby born with this condition is small, has a feeble cry, mottled skin, low-set and deformed ears, a receding chin, a rounded bottom of the foot, an index finger that tends to overlap the third finger, heart and kidney abnormalities, skeletal deformities, and mental retardation. The average life span is only about ten weeks. The frequency is about one in each 3000 live births and increases with maternal age.

Patau's Syndrome. This is sometimes called the D-syndrome because it results from trisomy of one of the chromosomes of the D group, that is, chromosome numbers 13 to 15. When the recent method of identification of chromosomes by banding was used, it was seen that chromosome 13 is the one involved. Infants having this syndrome characteristically have a broad nose, small cranium, small eyes that are usually nonfunctional, frequent cleft lip and palate, heart defects, and mental retardation. Early death comes to all. Their frequency is about one in 10,000 live births.

Other Human Aberrations. Many other types of aberrations have been observed. Investigators exploring the causes of mental defects have found numerous cases of ring chromosomes, isochromosomes, translocations, and simple deletions. It is apparent that any upset in the gene balance is going to affect the development of the brain along with any other defects that may result.

One might wonder about nondisjunction of the other chromosomes. Are they not also susceptible to this type of aberration? The answer is yes, but the results are so extreme that the embryos do not survive to a live birth. Trisomy of other chromosomes can be seen in karyotypes of spontaneously aborted fetuses. In general, the longer the chromosome involved, the earlier the abortion, but the specific genes involved play an important part. For instance, very few babies have been born with trisomy-22, for this is one of the shortest of the chromosomes. It must contain some very vital genes. Even the most frequent trisomy, that causing Down's syndrome, has a high rate of loss through abortion, and those that are born are only a fraction of those that are conceived.

About 40% of the spontaneously aborted fetuses show some type of chromosome aberration. Very few monosomics have been found, even in the earliest abortions. They should be produced in a frequency equal to the trisomics, but the condition evidently

causes such early death that they are seldom implanted in the uterus. Hence the total loss of conceived embryos as a result of chromosome aberrations must be great.

SYMBOLS FOR HUMAN CHROMOSOME COMPLEMENTS AND ABERRATIONS

At a Paris conference in 1971, leading cytogeneticists of the world gathered to devise symbols that could be used for chromosome complements along with any aberrations that might be present. Each chromosome was divided into a short arm, designated as p (from the French *petite*), and a long arm, designated as q. (All human chromosomes have one arm that is at least slightly shorter than the other.) A plus or minus sign is added after the letter to indicate an increase (translocation) or a decrease (deletion) in its length. For instance, a man with a deletion of chromosome 22 in his bone marrow would be symbolized as 46,XY,22q⁻. This means that the chromosome number is 46 and this includes X and Y, but one of the two chromosome 22s has a deletion of its long arm. A male with Klinefelter's syndrome who also has Down's syndrome would be 48,XXY,+18. Table 13–1 shows some typical symbols and their interpretation.

PROBLEMS

1. In *Drosophila* a trait known as Star eye (rough, irregular facets on the eyes) is due to a dominant gene *S* located at 1.3 on chromosome 2. In the offspring from a Star eye crossed with wild type there is one fly with normal eyes. Use a diagram to explain how this could happen as a result of chromosome aberration.

2. Linkage studies in maize show that the following genes are all on the second chromosome and in this order: white sheath, glossy leaves, silkless, and chocolate pericarp. In one variety, however, crossover studies showed the order to be white sheath, silkless, glossy leaves, and chocolate pericarp. Show how this might be explained.

3. Tetraploid islands of tissue are sometimes found in higher animals, but an entire animal with tetraploid cells is very rare. Explain why.

TABLE 13–1
HUMAN CHROMOSOME SYMBOLS AND THEIR INTERPRETATION

Symbol	Interpretation
46,XY	Normal male
46,XX	Normal female
45,X	Turner's syndrome
47,XXY	Klinefelter's syndrome
47,XX,+21	Female with Down's syndrome (one extra 21)
46,XY,5p−	Male with *cri du chat* syndrome (deletion from the short arm of one chromosome 5)
45,X/47,XXX	Mosaic female, some cells with single X and some with three X's
46,XY,t(8p−,5q+)	Male with translocation of part of the short arm of chromosome 8 to long arm of chromosome 5

4. How might a new species arise in nature from a combination of polyploidy and hybridization?

5. Why are allotetraploids more fertile than autotetraploids and both more fertile than triploids?

6. In *Drosophila* the fourth chromosome is so small that monosomy-4 flies can survive and reproduce. Show the genotype and phenotype of the offspring of an eyeless fly crossed with a monosomy-4 fly with normal eyes. Eyeless results from a recessive gene, *ey*, which lies on the fourth chromosome.

7. In rare cases females with Down's syndrome have achieved sufficient sexual maturity to be fertile. Twelve children from such females have been reported. About how many of these would you expect to have the syndrome?

8. Why are the chromosomes in *Drosophila* salivary gland cells so much longer and so much thicker than those in other somatic cells?

9. Ring chromosomes have been found in some patients in mental institutions. Why should this shape of chromosome result in mental defect?

10. Most cases of Down's syndrome have resulted from two 21s in the egg, but some types of this syndrome arise from both sperm and eggs equally. Explain.

14. GENES IN ACTION

We consider it marvelous that we can condense all the information of an encyclopedia into many volumes into a small roll of microfilm that can be held in one hand. Yet this miniaturization is quite gross when we consider that in the genes is compressed, within the nucleus of one microscopic cell, the great mass of information needed to construct such a complicated organism as the human body. In this chapter we shall consider the ways in which the information contained within the genes is translated into the production of living organisms.

THE GENETIC CODE

Modern espionage agents are experts in cracking the codes used by foreign governments to send secret messages. The genetic code has been much more difficult to decipher, but it has finally yielded its secrets to the continued probing of researchers.

Triplet Codons. A gene is made of a long double helix with cross connections of paired bases, the purines and pyrimidines, as described in chapter 3. The genetic code indicates the sequence of amino acids in the polypeptide chains that are produced in the cytoplasm—chains that form the proteins of the cell.

Three bases in a DNA molecule code one amino acid in a polypeptide chain. Since there are four kinds of bases—adenine, thymine, guanine, and cytosine—there are 64 possible triplet combinations ($4^3 = 64$). This is an ample amount to code the twenty different kinds of amino acids that exist. If we find that a cell produces a particular polypeptide chain of 150 amino acids, we know that the gene that coded this chain has 450 paired bases. The assemblage of amino acids into polypeptide chains, however, occurs in the cytoplasm at the site of small bodies, the **ribosomes,**

which are usually grouped together in chains to form **polyribosomes**. How can the genes in the nucleus influence the way amino acids are put together on these ribosomes?

Gene Messengers. The genes send messages out to the ribosomes by means of **messenger-RNA**, or **m-RNA**. RNA is a nucleic acid similar to DNA, but with three differences. First, the chains in RNA are single-stranded, not double-stranded as those in DNA. Second, the sugar in the backbone of the RNA strand is ribose sugar rather than deoxyribose sugar. Both are pentose sugars, but ribose sugar contains more oxygen, as its name indicates. Third, one of the four pyrimidine bases in RNA is **uracil** rather than thymine. The other three bases are the same as in DNA.

When a gene is to produce m-RNA, the two DNA strands separate at their weak hydrogen bonds as if the gene were going to replicate. Instead of replicating, m-RNA is formed along one of the two strands. It is a complementary replication with thymine attracting adenine, cytosine attracting guanine, guanine attracting cytosine, but adenine attracting uracil. Ribose sugar and the connecting phosphate groups complete the RNA molecule. Only one side of the DNA molecule is used to produce the m-RNA, and this side is used all the time. (A very different message would be coded if it were produced by the other side.) The m-RNA then passes out of the nucleus through one of the pores in the nuclear membrane and moves to a polyribosome. The ribosome contains some RNA (**r-RNA**), and this seems to be the attractive force which brings the m-RNA to it.

Transfer-RNA. Another type of RNA must be involved in producing polypeptide chains, because the amino acids lie free in the cytoplasm and must be transported to the ribosomes. This task is accomplished by **transfer-RNA** (**t-RNA**). A t-RNA molecule is a single strand doubled back on itself to form a cloverleaf shape. At the open part of the molecule, one end extends out with the single bases, cytosine, cytosine, and adenine. The other free end is shorter and contains only guanine. At the upper twist there are also three bases that are not paired. These bases vary, different combinations carrying different amino acids. If the bases are cytosine, cytosine, and uracil the molecule would pick up the amino acid glycine. This t-RNA molecule will fit into the m-RNA at the codon GGA, which contains its complementary bases. It releases its glycine at this point and is free to move away and pick up an-

other molecule of glycine and bring it to the same or a different polyribosome.

Polypeptide Chain Formation. The sequence of events in protein synthesis is as follows. A gene is stimulated to open up and make a molecule of m-RNA, which moves out of the nucleus through one of its numerous pores. In the cytoplasm, this m-RNA contacts a polyribosome that can consist of from five to several dozen ribosomes. The m-RNA moves across these ribosomes in a manner that may be compared to a computer tape transmitting its message. At the same time the t-RNA molecules are bringing in the amino acids and depositing them in a sequence determined by the code on the m-RNA. The polypeptide chain that is formed may be a protein or it may combine with other chains to form the protein to be constructed.

Deciphering the Code. The synthesis of polypeptide chains can take place outside the cell if the necessary parts are present. The m-RNA taken from a human cell is placed in a mixture of ribosomes, t-RNA, and enzymes from bacteria. Then amino acids are added, along with a little ATP for energy. Soon polypeptide chains
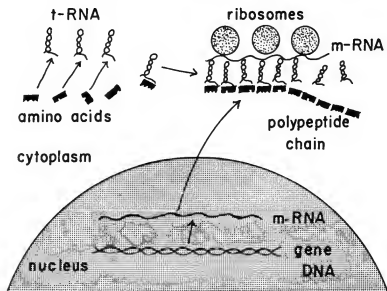
Fig. 14–1. How genes direct the formation of polypeptide chains in the cytoplasm.
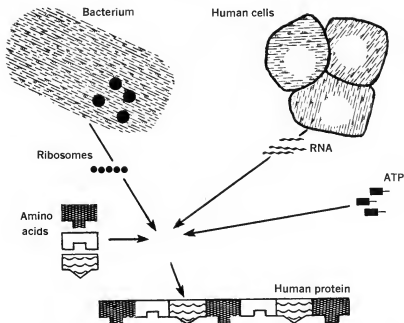
Fig. 14–2. The ribosomes from bacteria can produce human protein when messenger-RNA from human cells is present. (From Winchester, Biology, Van Nostrand.)

are formed that are characteristic of the human cell, indicating that it is the m-RNA that determines the type of protein produced.

In determining the codes for the different amino acids, investigators substitute m-RNA produced in the laboratory for that produced in cells. When only uracil was used to make this synthetic m-RNA, the chain formed consisted only of the amino acid phenylalanine. Hence it was evident that the **codon** (base triplet) for phenylalanine is UUU. By using other single-base synthetic m-RNA and then adding different combinations of bases, it became possible to determine the codons for each of the amino acids. Table 14–1 shows that most amino acids can be coded by more than one triplet codon. It will be noted, however, that the first two letters are the same for any one amino acid, with only a few exceptions. It is the third letter that varies in most cases. Keep in mind that these codons are expressed in terms of the triplets on m-RNA. The genes and t-RNA would have the complementary bases.

TABLE 14–1
THE GENETIC CODE

Codons in Messenger-RNA	Amino Acid Coded
GCU GCC GCA GCG	Alanine
CGU CGA CGG CGC AGA AGG	Arginine
AAU AAC	Asparagine
GAU GAC	Aspartic acid
UGU UGC	Cysteine
CAA CAG	Glutamine
GAA GAG	Glutamic acid
GGU GGC GGA GGG	Glycine
CAU CAC	Histidine
AUU AUC AUA	Isoleucine
UUA UUG CUU CUC CUA CUG	Leucine
AAA AAG	Lysine
AUG	Methionine
UUU UUC	Phenylalanine
CCU CCC CCA CCG	Proline
UCU UCC UCA UCG AGU AGC	Serine
ACU ACC ACA ACG	Threonine
UGG	Tryptophan
UAU UAC	Tyrosine
GUU GUC GUA GUG	Valine
UAA UAG UGA	Terminator codons
AUG	Initiator codons

Initiator and Terminator Codons. The DNA molecule seems to be one long chain consisting of many individual genes. We might compare the molecule to a page in a book. The genes would be analogous to the sentences on the page, while the codons would correspond to the words within the sentences. On the printed page we do more than just put down the words. We use a capital letter to start a sentence and a period, or other punctuation mark, to indicate the end. Likewise, the gene must be set apart somehow so that, as m-RNA is formed, it will begin at the proper place and end at the proper place. Should a beginning be made just one base behind the proper joint, the entire code would be greatly altered. An initiator codon lies at the beginning of a gene to indicate the place for m-RNA formation to start. It is just as important

for the m-RNA formation to stop at the end of the gene and not go on transcribing codons from the adjacent gene. Terminator codons at the end of the gene signal the place for m-RNA to stop.

CONTROL OF GENE ACTION

Once the mechanism of gene action was understood, attention turned to the problem of its control. Obviously, if all genes were to produce their m-RNA continuously, the result would be just a mass of protoplasm without differentiation. Most of the genes in your body at this time are inactive. Probably no more than 5% of them are producing m-RNA. Some of the genes in your cells will never open again and produce m-RNA. They played a role in your early development, but once you became an adult they closed permanently and will never function again in your somatic cells. Should you pass such genes on to offspring, however, they will again do their part in building a new body. Other genes function off and on according to need. Your skin is continually being shed and replenished at a slow rate, but should your skin receive an injury, the genes that cause growth and division of these cells become quite active until the injured region is healed, then they lapse back into their former rate. The genes that produce the extracellular enzymes of digestion remain closed when there is no food to be acted upon, but once you begin eating they start producing the enzymes needed to digest the food. An efficient method of homeostatic control accounts for this orderly function of the genes according to need for their products.

The Operon Theory. Studies on the action of genes in the bacterium *E. coli* by Jacob and Monod led to the formulation of the operon theory to explain the method of control over the genes' activities. This theory postulates three kinds of genes: structural, operator, and regulator genes. The genes that produce m-RNA are the **structural genes.** A group of such genes having related functions lie in sequence on the chromosome. Adjacent to each group of structural genes is an **operator gene,** which acts as the "switch" to turn on the functional genes and cause them to produce their m-RNA. This entire unit of structural genes and its operator makes up an **operon.** At another site on the chromosome is a **regulator gene** that produces a **repressor substance,** which inhibits the

operator gene. The repressor molecule has two active sites, one that can unite with the operator gene and one that can unite with a specific effector. If the effector is present, the repressor unites with it and then loses its ability to unite with and inhibit the operator gene. With the repressor inactivated, the operator gene is left free to stimulate the structural genes into action. Thus, the effector is the ultimate controlling agent. With the effector present, m-RNA is produced; in its absence, no m-RNA is produced. This effector may diffuse into the cell from the outside, or it may be produced within the cell.

The lactose operon of *E. coli* is an example of this mechanism. At least two structural genes in the operon are related to the utilization of beta galactoside, commonly known as lactose or milk sugar. As long as there is none of this sugar within the cell, there is no need for an enzyme to break it down. No enzyme is produced because the repressor is united with the operator. When lactose is present, however, the sugar acts as an effector and blocks the repressor. As a result, the operator gene is free to stimulate the two structural genes to release their m-RNA. One of these genes produces m-RNA that codes the production of the enzyme beta galactosidase, which breaks down the lactose into glucose and galactose. The other structural gene produces m-RNA that codes the production of galactoside permease, which makes the plasma membrane of the cell more permeable to lactose. The cell can therefore absorb the lactose more rapidly. Once the available lactose has been used up, the repressor is no longer inhibited, and the two structural genes cease their production of m-RNA, which codes the production of the two enzymes.

A mutation of any one of these genes can alter the reaction. The regulator gene may, after mutating, no longer be able to produce an effective repressor; consequently, the structural genes produce the enzymes even though no lactose is present. The operator gene may undergo a mutation that renders it incapable of stimulating the structural genes to produce enzymes even in the presence of lactose. A mutated structural gene may produce a protein sufficiently different so that it cannot function as an enzyme.

The enzyme may be produced when there is no effector, but as the effector builds up within the cell, the enzyme production stops. In *Salmonella typhimurium,* a close relative of *E. coli,* ten structural genes are in an operon and each of these genes produces an
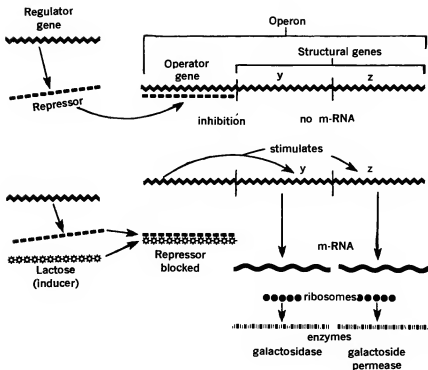
Fig. 14–3. Gene control through operon, regulator and inducer. This diagram illustrates an operon of E. coli that controls genes which code the production of two enzymes which react with lactose.

enzyme required in the series of reactions that synthesize the amino acid histidine. When this amino acid is deficient in the cell, the enzymes are produced. As the histidine accumulates and a sufficient quantity is present, however, the genes cease producing the m-RNA to code the production of the enzymes. In this type of system, the repressor substance inhibits the operator gene only when it is combined with histidine.

Certain antibiotics have value in treating infectious diseases because they inhibit the growth of bacteria and other microorganisms. Such inhibition has proved to be due to an inhibition of m-RNA synthesis. Without these messages to the ribosomes, there is a reduction in protein production and bacterial growth slows. The body then has a better chance of destroying the invaders. The antibiotics seem to act as repressors which prevent the operator genes from stimulating the structural genes.

Carcinogenic agents are substances that cause cancer. Some evidence indicates that they act as effectors, blocking repressors of operator genes which stimulate the structural genes that code the synthesis of proteins needed for growth. With repressors blocked, these genes continue to code the production of more and more of these proteins, resulting in uncontrolled growth of the cells. The application of the antibiotic actinomycin-D to the skin of experimental animals prevents the carcinogenic action of some of these agents. We can also see how any mutagenic agent which could change repressor genes could also result in uncontrolled cell growth and cancer. In general, mutagenic agents are also carcinogenic.

Although the evidence of operon control of gene action in higher organisms is not so well documented as in the bacteria and other lower organisms, the pattern appears to be the same. Hormones in both plants and animals seem to serve as effectors that can unite with repressors and allow certain structural genes to function. Human tissue culture cells from the uterus show greatly increased m-RNA output when the female hormone estrogen is added to the culture. Vitamins seem to serve as effectors that stimulate certain gene actions. Vitamin D, for instance, seems to turn on the genes for the production of calcium-binding proteins that are necessary for normal bone growth.

Chromosome Puffs. The giant chromosomes from the salivary glands of *Drosophila* and other dipteran insects show regions that are swollen and diffused. These so-called puffs are not always at

the same place. At one stage of larval development certain parts of the chromosomes are puffed; at other stages these areas are retracted and other regions are puffed. When the chromosomes are stained with dyes that are specific for RNA, the puffed regions stain most heavily, indicating that these are the regions of greatest gene activity. The incorporation of radioactive uracil, the base that is in RNA but not in DNA, shows the heaviest uptake of the radioactive particles at the puffs. Administration of actinomycin-D to the larvae before removal of the salivary glands results in a reduction in the puffs and the administration of certain hormones increases them. The molting hormone **ecdysone** can be injected into the larvae of *Drosophila*. When the glands are removed and studied a short time later, puffs are seen near the terminal end of chromosome 3. These puffs are not present in uninjected larvae. Hence it can be concluded that this region of the chromosome contains genes that function during the molting process.

Role of Histones. Associated with DNA in the chromosomes are proteins known as histones. About five different types of histones have been identified. The fact that the puffs of salivary
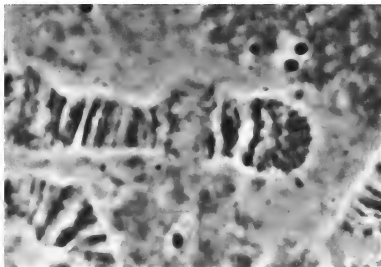
Fig. 14–4. Chromosome puffing in Drosophila salivary gland chromosome. Near the center of the photograph the chromosome is swollen and indistinct. Evidence indicates that puffing is caused by an uncoiling of the DNA strands and an output of m-RNA.

gland chromosomes are low in histones while the rest of the chromosomes are rich in these proteins indicates that histones are suppressors of gene activity. When James Bonner removed histones from the embryos of germinating garden peas he found that the production of m-RNA increased about fourfold. The addition of extra histones extracted from other embryos resulted in a reduced output of RNA. One suggestion is that the histones, along with the repressor, may be required to inhibit the operator genes.

GENE FUNCTION THROUGH ENZYMES

We have already seen that genes code the production of proteins. Some proteins, perhaps about 30%, are structural proteins which increase the protoplasm in the cell and thus contribute to growth. The remaining 70% or so produce functional proteins, or enzymes. A few of these are extracellular enzymes that pass out of the cell and produce their effect elsewhere. Enzymes in the human digestive tract, for example, convert digested food into a form that the body can absorb. The great majority of enzymes, however, are intracellular; they remain within the cells and exert their catalytic action there. The number of these enzymes is enormous; over 20 separate enzymes, for instance, are required to break down the simple sugar glucose and make its energy available to the cell. Hence there must be many thousands of such enzymes and a deficiency of even one of these can result in serious consequences.

Enzymes in *Neurospora*. G. W. Beadle and E. L. Tatum received the Nobel Prize in 1958 for their pioneer work on genes and enzymes in the pink mold *Neurospora*. This rather remarkable organism can live on a culture medium with the barest of nutrients. Only a few simple salts, sugar, ammonia, and a single vitamin (biotin, a B vitamin) are necessary for the growth of the wild type of this mold. This does not mean that *Neurospora* does not need other amino acids and vitamins; it can synthesize its own by means of its enzyme system. Hence *Neurospora* has many enzymes that we do not possess because we must ingest most of the amino acids and vitamins in our food.

Because *Neurospora* is haploid, and all genes are expressed, mutations are easily detected. For example, one gene produces the

enzyme tryptophan synthetase, which causes indol and serine to combine to form the amino acid tryptophan. A mutant form of the gene apparently cannot produce the enzyme, at least not in its functional form, so a mold having this gene cannot live on a medium which does not contain tryptophan. Reverse mutations of the mutant gene back to the wild type occur in rare instances. These, too, are easy to detect. Millions of spores from the mutant
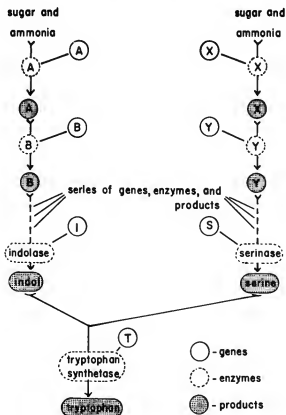
Fig. 14–5. An enzyme series in Neurospora which leads to the production of tryptophan.

strain can be placed on a medium containing serine and indol, but no tryptophan. If any of the spores contain reverse mutations, they will grow into colonies. Thus, if such reverse mutations occurred only one time in several million spores, they could be detected and colonies established from them.

There is usually not one, but a series of enzymes and reactions in most of the processes of synthesis or degradation that occur within the cell. Indol and serine are the products in the series that are formed just before tryptophan production. When the mold is grown on a minimal medium, both the serine and the indol must be synthesized before tryptophan can be produced. A series of reactions is required for the synthesis of each of these substances, and a mutation of a gene responsible for any one of the enzymes involved would make tryptophan production impossible.

A Human Enzyme Series. It is much more difficult, of course, to trace the action of genes through enzymes in human beings, but the biochemical techniques have been so refined that many rather detailed pathways have been uncovered. The idea that deficiency of cellular enzymes could cause human abnormalities was first proposed by an English physician, A. E. Garrod. Certain babies in his care produced urine that turned black upon exposure to light and air. He found that this urine contained much greater than normal quantities of homogentisic acid, also called alkapton. He reasoned that this disorder, known as **alkaptonuria**, resulted from the lack of an enzyme necessary for the breakdown of alkapton. He also noted excesses of phenylalanine and phenylpyruvic acid in the urine of patients with **phenylketonuria (PKU).** He published his conclusions in 1909 in a book, *Inborn Errors of Metabolism.* It was not until Beadle and Tatum made their findings in 1950, however, that the importance of Garrod's findings were realized. Now we know that many human abnormalities result from enzyme blocks.

A human enzyme series can be illustrated by the breakdown of two amino acids, **phenylalanine** and **tyrosine,** which are present in most protein foods. A protein is digested in the intestine and broken down into its component amino acids. These are absorbed and transported to the cells by the blood. Three different enzymes may act upon phenylalanine within the cells. One enzyme combines it with other amino acids to form cell proteins. Another enzyme converts it into phenylpyruvic acid which then passes through a
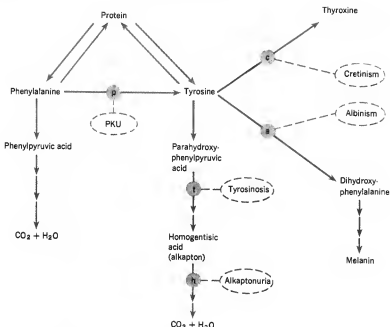
Fig. 14–6. A human enzyme series involving the breakdown and conversion of two amino acids, phenylalanine and tyrosine. (From Winchester, Genetics, 2d ed., reprinted by permission of Houghton Mifflin.)

series of other enzyme-mediated changes. A third enzyme, in the major metabolic pathway, converts it into tyrosine, another amino acid. About one child out of each 10,000 born receives a pair of recessive genes that cannot produce the latter enzyme. In such babies phenylalanine has only two pathways. A relatively small amount is required to synthesize cell proteins. Some of the excess will go to form phenylpyruvic acid, but more than the body requires will be produced. This extra acid and the large amount of unconverted phenylalanine build up in the blood. The kidneys can remove some of this excess, but the blood level of the two substances remains high unless the intake of phenylalanine is greatly restricted.

At birth a baby with PKU appears normal because the mother's enzyme can make the conversion of phenylalanine to tyrosine in her liver cells. After birth, however, the phenylalanine level rises rapidly in the baby's blood. It may reach as high as 60 mg per 100

ml of blood compared to about 2 or 3 mg in a normal child. In some way this excess of phenylalanine interferes with brain development. One theory is that it so floods the cells with this amino acid that there is a deficiency of certain other vital amino acids. The result is retarded mental development.

PKU can be prevented in individuals homozygous for the gene by restricting phenylalanine in the diet to the amount required to produce the cell proteins, leaving little left over to build up in the blood. Special powdered preparations of amino acids, omitting phenylalanine, are given along with low protein foods such as fruits and certain vegetables. Successful management of PKU patients involves regulating phenylalanine to just the right amount; too little can also cause damage. A normal diet can be started at about eight years of age because by that time the brain is well developed and no damage seems to result from an excess of phenylalanine in the blood. A woman with PKU will have to resume the restricted diet if she ever becomes pregnant because the excess phenylalanine in her blood would damage the brain of her fetus.

Early recognition of PKU is vital because the brain damage is irreversible. The Guthrie test currently used can be done on blood as early as the third day after birth. A drop of blood on filter paper is placed on a plate seeded with bacteria that require phenylalanine. A heavy growth around the blood indicates high phenylalanine in the blood. Many states now make this test mandatory for all newborn babies at about the third day of extrauterine life.

Tyrosine may follow several metabolic pathways of conversion depending on the enzymes that act upon it. First, it may be used in the construction of cell proteins. Second, it may be used in the production of thyroxine in the thyroid gland. Enzymes alter the tyrosine molecule and combine it with iodine to make this hormone which regulates the rate of metabolism. A dominant gene codes the production of thyroxine, and individuals homozygous for its recessive allele cannot produce this hormone in a proper form. They receive the hormone from the mother before birth, but within a few months show retarded mental development and a possible enlargement of the thyroid gland. They are said to have **genetic goiterous cretinism.** Without treatment they will be greatly retarded mentally, physically, and sexually. Thyroid hormone can be used to prevent these symptoms.

Another series of enzymes, acting upon tyrosine, leads to the

production of **melanin,** the brown pigment that gives color to the skin, hair, and eyes. A recessive gene fails to produce one of the enzymes in the series and no melanin can be produced. The result is **albinism.** Another type of albinism results from another recessive gene that slows the absorption of tyrosine by the cells. With insufficient tyrosine, little melanin is produced, but there is some.

Finally, most of the tyrosine is acted upon by enzymes that convert it into parahydroxyphenylpyruvic acid which another enzyme changes to homogentisic acid (alkapton). A recessive gene that cannot produce this enzyme causes a buildup of excess tyrosine; such a condition is known as **tyrosinosis.** The tyrosine in the urine will be abnormally high, but there is no great body defect.

Another recessive gene is responsible for a break in the chain after alkapton has been formed. This results in **alkaptonuria,** as was first described by Garrod. Not only is alkapton abundant in the urine, but it also accumulates in cartilages. This deposit seems to do no harm early in life, but with maturity it causes some disfigurement because alkapton turns black in the cartilages exposed to light. Hence, the ears and the tip of the nose will become darkened. Also, the accumulation of alkapton in the cartilages at the joints may result in a painful type of arthritis.

Ways Enzyme Deficiencies Cause Defects. Enzyme deficiencies can cause defects in several ways. First, the substance acted upon by the enzyme may build up to an abnormally high level which can do damage. The excess of blood phenylalanine in those with PKU is an example of this. **Galactosemia** is another example. Some babies are homozygous for a recessive gene responsible for an inability to produce one of the enzymes necessary for the breakdown of lactose, or milk sugar. Galactose phosphate, an intermediate product in the series, is the one that cannot be broken down. The buildup of this substance results in a bloating of the liver, vomiting, loss of weight, cataracts, and mental retardation. Death comes within a few months if nothing is done. Since lactose comes almost exclusively from milk, however, we can prevent all these symptoms by simply taking the baby off milk as soon as the symptoms appear.

The second way that some defects may arise is by the lack of an end product of enzyme conversion. Cretinism is a good example of this type. These defects can often be treated by administration of the product.

Third, a defect can arise because of the accumulation of an excess of a product produced in an alternate pathway. With PKU there is a buildup not only of phenylalanine, but also of phenylpyruvic acid. Normally, only a little of the phenylalanine is converted into this acid, but with a great excess of phenylalanine this alternate pathway is stepped up, and more of the acid is produced. A similar situation occurs in **hyperuricemia** and **gout**. The normal pathway of excretion of nitrogenous wastes is through urea. Other enzymes can carry these wastes, to uric acid, but this is a minor pathway in most people. When there is an enzyme break for the normal production of urea, however, much more waste than usual is converted into uric acid. The high concentration of uric acid in the blood can cause trouble. Uric acid can unite with sodium and form sodium urate crystals which may accumulate in the joints and cause the painful affliction known as gout. If an excess of uric acid is present from childhood there will be great mental retardation in the condition known as hyperuricemia. Other genes can cause these conditions, including one which prevents the normal rate of absorption of uric acid by the kidneys.

A question often asked is, why cannot we prevent all enzyme deficiency-caused defects by injecting the missing enzyme? Unfortunately, enzymes are proteins and protein molecules are generally too large to pass through the plasma membranes that surround cells. Even so, such treatment has been tried with the hope that there just might be some way the cells could take in the enzymes. Injections of the enzyme hexosaminase-A, which is the enzyme missing in Tay-Sachs disease, however, failed to relieve the progressive nerve deterioration characteristic of this disease.

CYTOPLASMIC GENES

When genes were first found to be associated with the chromosomes, it was assumed that all genes were on the chromosomes. Continued investigation showed that some DNA was located in the cytoplasm. The mitochondria, for instance, are cytoplasmic bodies that contain some DNA and have a self-replicating system independent of the chromosomes. Kinetoplasts, small bodies that produce the cilia of certain protozoa, are also in this category. Plastids of plants are also included. A few cases will serve to illustrate.

Plant Plastids. The cytoplasm of most plant cells contains plastids, the centers of important physiological conversions. The best-known plastids are the chloroplasts, which are centers of photosynthesis. The cytoplasm of the ovule contains primordial plastids. These are not generally brought in by the male nucleus that fertilizes it; hence inheritance of the type of plastids is primarily from the female line. The four-o'clock, *Mirabilis jalapa,* sometimes has variegated leaves with areas of pale green or white as well as the normal green. The cells of these pale areas have plastids that fail to develop the green chlorophyll or develop only a small amount of it. The transmission of this trait is solely through the female. The ovules of a flower growing on a pale green branch will produce seed which grow into plants that are pale green all over no matter what type of pollen fertilized the ovules. Ovules from variegated branches yield three types of offspring: green, pale green, and variegated. The ovules carry the plastid primordia which grow into chloroplasts with characteristics of the branch upon which they were borne.

Yeasts. Ephrussi discovered one strain of yeast that was red in color, in contrast with the normal, colorless strain, usually called white. Because the red strain originated after treatment with mustard gas (a mutagenic agent), it was assumed that it resulted from a nuclear gene mutant. However, when the yeast was grown under optimum conditions where growth was very rapid, some white colonies appeared. Surely there could not be so many reverse mutations. Actually, the gene for red pigment was located in the cytoplasm. Yeasts reproduce asexually by budding. A bit of the cytoplasm, along with a nucleus formed by mitosis, pinches off from the larger cell. When growth is very rapid the duplication of the genes for the red pigment may not keep up with the growth and budding of the cells and some buds may, by chance, fail to receive any of the genes for red pigment. These buds grow into white colonies.

Other cytoplasmic genes in yeast have been identified. One of these is for *petite,* a trait characterized by the small size of the colonies. They lack certain mitochondrial enzymes and cannot convert food into energy as well as do normal mitochondria.

Paramecium. An interesting case of apparent cytoplasmic inheritance in *Paramecium* was found by T. M. Sonneborn of Indiana University. He observed that some paramecia (killers)

Usual conjugation

Nuclear material only exchanged

Rare conjugation where some cytoplasm is exchanged

Some kappa comes into cytoplasm of sensitive

Fission

More fission

All killers All sensitives All killers
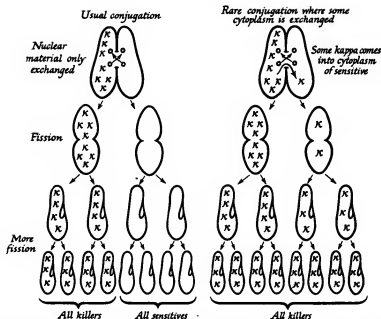
Fig. 14–7. In Paramecium a sensitive strain can be converted into a killer strain by the cytoplasmic transmission of the kappa factor from a killer during conjugation. (From Winchester, Genetics, 2d ed., Houghton Mifflin.)

produced a substance known as **paramecin** which could kill other paramecia (sensitives) that do not produce this substance. The killers were found to contain cytoplasmic bodies, **kappa**, which produce paramecin. This killer trait was transmitted through the cytoplasm. During conjugation of a killer with a sensitive, some of the kappa in the cytoplasm could pass into the sensitive along with the nuclear gene, thus converting the sensitive into a killer. When all the evidence was assessed, however, it was concluded that the kappa was actually a virus-like body and not a true plasmagene.

Chlamydomonas. Investigations by Ruth Sager on the green alga *Chlamydomonas* also showed cytoplasmic inheritance. This one-celled organism is haploid, but at times two cells of opposite sex unite to form a diploid zygote. Meiosis takes place and four haploid cells are produced from the zygote. Two of these haploid cells will be female and two will be male because of a nuclear gene

which determines sex. When sexual union occurs, both male and female cells contribute cytoplasm, but inheritance of cytoplasmic factors takes place mainly through the female cell. Perhaps the male cytoplasmic factors are cast off during divisions of the zygote in meiosis. Such characteristics as streptomycin resistance have a pattern of inheritance which indicates that they are transmitted through cytoplasmic factors.

PROBLEMS

1. What problems would arise if we had doublet rather than triplet codons for the amino acids in the genetic code?

2. Suppose the first codon after the initiating codon in a gene is ATC. What would be the codon at the beginning of the messenger-RNA made from this gene? What would be the codon on the transfer-RNA which would fit into this messenger-RNA at this point?

3. Suppose you make a tissue culture from the skin cells of a guinea pig and compare it to tissue cultures made from human skin cells. Would you expect to find that the transfer-RNA is the same in the two types of cells? Would the messenger-RNA be the same in the two? Explain.

4. The beta chain of the human hemoglobin molecule contains 146 amino acids. How many nucleotide pairs would you expect in the gene which codes the production of this chain, exclusive of initiator and terminator bases?

5. Most people have at least one dominant gene for the production of an enzyme which can break down the amino acid cystine. This enzyme is produced in the liver cells only when the amount of cystine in the blood becomes higher than normal. Explain exactly how the gene for the production of this enzyme might be activated when the enzyme is needed and deactivated when the enzyme is no longer needed.

6. Many antibiotics have been discovered which are very effective in slowing the growth of bacteria, but they cannot be used to treat human diseases because of harmful effects on the body. How might these cause damage and why are some antibiotics not harmful to man, but still inhibit bacterial growth?

7. Suppose a mutation inactivated the operator gene of the lac-

tose operon of *E. coli.* How would the bacterium then react to the presence of lactose in the medium?

8. Some albinos will develop a darker skin if they are fed extra quantities of tyrosine. Explain how this can be possible.

9. A woman was born with PKU, but through diet in her early life she was saved from being mentally defective. She now eats a normal diet, but her doctor warns her that she must go back on the low phenylalanine diet if she ever becomes pregnant. Explain.

10. When a baby has galactosemia we can prevent damage from the enzyme deficiency, yet when a baby has alkaptonuria there is nothing we can do to keep homogentisic acid from accumulating in the cartilages. Explain why damage can be prevented in one condition but not in the other.

11. Suppose you find a branch of a tree that has leaves of a peculiar yellow-green color. Someone suggests that this may be due to mutation of a cytoplasmic gene. How would you determine if this was true?

15. MUTATION

We have long known that in any pure-breeding variety of plant or animal, an occasional individual appears that is different from its parents and can transmit this difference to offspring. Frequently, the new trait is due to the expression of a recessive gene that has been present in the stock for a long time and becomes homozygous in this individual. Sometimes, however, the trait is due to a recent change in a gene. When the new trait is desirable, it can be established by selective breeding in the entire stock. It is through such selection of new and desirable traits that many of our domestic animals and cultivated plants have been improved.

In 1791 a New England farmer, Seth Wright, noticed a ram in his flock with unusually short legs that could not jump over fences. He bred the ram and, by repeated inbreeding and selection, soon had an entire flock of these short-legged sheep, which have since become known as the ancon breed. The trait was due to a recessive mutation of a single gene that appeared in the flock and became homozygous in this ram. Such mutations are even easier to establish in plants because they can be propagated asexually by cuttings, grafting, bulbs, or corms. Navel oranges and seedless grapes had their origin in the expression of mutations on single branches. Many beautiful varieties of tulips, orchids, and other flowers are the result of mutations.

In 1901 Hugo De Vries used the word *mutation* to explain the appearance of deviant forms of evening primroses (see chapter 2). His mutations were actually due to chromosome aberrations, not to changes in genes, to which the term is now generally restricted.

Mutations are of great evolutionary significance. They provide the variety that is necessary for natural selection. The majority of mutations are harmful, however, because the species alive on earth today have already survived the rigors of the struggle for existence.

Fig. 15–1. The ancon mutation in sheep. The ram on the left and the ewe on the right are homozygous for this mutant gene and have the short legs characteristic of the ancon breed. (Courtesy Life magazine.)

Any random change in something that is already very efficient is most likely to be harmful, but in rare cases a mutation will be beneficial. Through natural selection such a mutation can be established in a species, just as through artificial selection we can promote the mutations we desire in domestic animals and cultivated plants.

THE METHOD OF MUTATION

Just what happens to a gene when it undergoes mutation? Genes replicate each time a cell divides, and each gene makes a perfect copy of itself through thousands of such replications. On rare occasions, however, a copy is made that is not an exact replica of the original. The situation might be compared to that of a very efficient typist copying a sentence over and over again. He might copy the sentence perfectly a thousand times, and then strike one letter that is wrong. This might change one word and, if it were a critical word, change the meaning of the entire sentence. Likewise, the DNA molecule of a gene duplicates itself exactly most of the time, but out of many thousands of such replications one molecule may be produced having one base that is different from its predecessor. This results in an alteration of one triplet codon, which may cause one different amino acid to be inserted in the polypeptide chain formed. In some cases the alteration may be
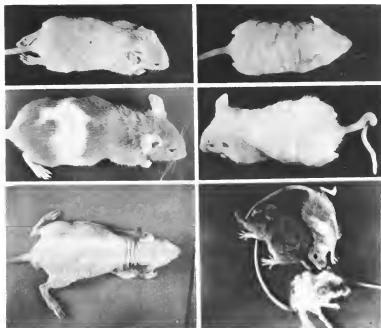
Fig. 15–2. Some mutant traits in mice. From left to right and top to bottom these are: short ear, waved fur, belted body, kinky tail, hairless body, and jittery nervous system. (Courtesy George Snell.)

critical and the mutant gene can have a marked phenotypic effect. The mechanism can be better understood by an actual example.

Human Hemoglobin Mutations. The normal adult hemoglobin molecule has a center containing iron, from which radiate two pairs of chains of amino acids. One chain, the **alpha chain**, contains 141 amino acids, while the other, the **beta chain**, has 146 amino acids. In a mutant form of the hemoglobin one of the 146 amino acids in the beta chain is different: Valine has been substituted for glutamic acid. This small alteration has far-reaching effects. Glutamic acid has a negative charge, but valine is neutral. Because of this change in their electrophoretic properties, the mutant hemoglobin molecules tend to form rigid chains when the oxygen level becomes low. This distorts the red blood cells into sickle shapes which do not carry oxygen very well. A person with this type of hemoglobin is said to have sickle-cell anemia and is likely to die early in life because of oxygen deficiency.
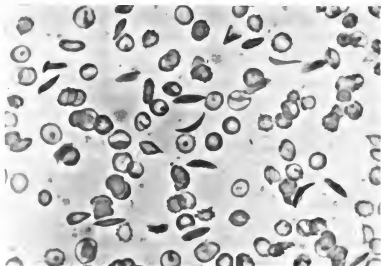
Fig. 15–3. Blood from a person with sickle-cell anemia. Many of the red blood cells are distorted into sickles because of the change of one amino acid out of 287 in the hemoglobin molecule.

The difference between the two types of hemoglobin can be demonstrated by electrophoresis. A drop of normal hemoglobin, hemoglobin A, can be placed on a paper moistened with a buffer solution and exposed to an electrical field. The overall charge of the hemoglobin is negative, so it moves toward the positive pole. When a drop of blood from a person with sickle-cell anemia is placed on such paper, however, the hemoglobin S moves more slowly because this hemoglobin has lost one of its negative charges. Blood from a heterozygous person will separate into two masses, one fast-moving and one slow-moving. This shows that both types of hemoglobin are present, an intermediate effect on the cellular level.

An ingenious method to determine the exact amino acid that had been altered was worked out by V. M. Ingram. He first exposed the hemoglobin to the enzyme trypsin, which breaks the chains wherever lysine and arginine are adjacent. The trypsin broke the beta chain into 28 peptides which could be separated by electrophoresis since each peptide was composed of a different set of amino acids. Hemoglobin S had one peptide, peptide 4, which was in a position different from peptide 4 of hemoglobin A. This peptide was cut out and exposed to another enzyme which broke it

into individual amino acids. These amino acids were separated by paper chromatography. Only one was found to be different between the two types of hemoglobin. Valine, instead of glutamic acid, was at position 6 in this peptide.

Later it was found that in one part of west Africa some people had hemoglobin C. This causes a mild anemia, less severe than hemoglobin S. An analysis of hemoglobin C showed that it migrated even more slowly than S in an electrical field. A separation of amino acids showed that lysine, which has a positive charge,
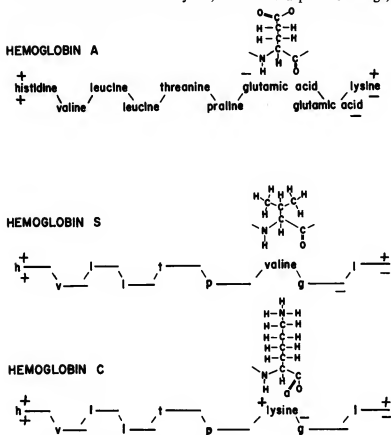
Fig. 15–4. Differences in peptide 4 for three varieties of human hemoglobin. Valine is substituted for glutamic acid in hemoglobin S and lysine is at this same position in hemoglobin C. All the other peptides are the same in all three.

was substituted for glutamic acid at the same sixth position in peptide 4.

With this information it became possible to determine just how these mutant forms of hemoglobin might have arisen. One of the m-RNA codons for glutamic acid is GAA, which would be CTT in the gene. If one base pair were reversed so that the side of the gene which codes m-RNA became CAT, the codon would then be for valine. This alteration of one out of the 424 bases that code the beta chain would result in the enormous phenotypic difference between a person homozygous for the mutant gene and a person homozygous for the normal gene. Hemoglobin C could have arisen by a substitution of T for C in the same codon, yielding TTT, a codon for lysine.

When hemoglobin from normal persons was subjected to the same analysis of amino acid composition, more variants were found. First, hemoglobin G was identified which had glycine instead of glutamic acid at the seventh position of peptide 4. Then other variants were found in both alpha and beta chains until substitutions had been found in all but a few positions of both chains. These discoveries brought out an interesting fact. Many mutations may occur without altering the product of the genes sufficiently to cause any phenotypic effect. Such **neutral mutations** can be detected only by special techniques which show the differences in the amino acid chains of the polypeptides.

With this information, plus that gained from studies of many other organisms, it appears as if alteration of the base sequence is the method of mutation. A base may be turned around so that it is in a reverse position, or one base may be substituted for another possibly during the replication process. It also has been shown that bases may become joined side by side so they cannot replicate properly. This is most likely to happen when two thymines are adjacent.

Reverse Mutations. Once a gene has mutated and becomes established in its mutant form it is stable and can replicate itself over and over again. We often refer to the deviations from the wild type (or normal) as mutant genes, even though the mutations that produced them occurred many generations previously. In the course of the countless replications, however, it is possible that one of the mutant genes will undergo a base alteration which will restore it to the original condition. Such reverse mutations are

much less common than direct or forward mutations. All the bases of a gene are open to alteration and any such alteration can result in a mutation. For a reverse mutation, however, a particular base must be involved. Studies made by the author on reverse mutations of six recessive mutant genes on the X chromosome of *Drosophila* showed an average frequency of reverse mutations which was only about 8% as great as the direct mutations of the same genes.

Reverse mutations are much easier to detect in microorganisms because they are haploid and can be raised by the millions. In *Neurospora* a mutation has been found that cannot produce an enzyme needed to synthesize adenine, one of the purines needed to produce both DNA and RNA. A strain of the mold with this mutation can live only on a medium containing adenine. M. Westergaard found one colony of this mold growing on a plate without adenine which had been seeded with about 600 million spores. Thus we can assume that the reverse mutation rate of this particular gene is about one in 600 million. When the mutagenic chemicals hydrogen peroxide and formaldehyde were added to the plate, the number of colonies that grew was greatly increased. One such plate showed 47 colonies.

KINDS OF MUTATIONS

A person unfamiliar with genetics may have the mistaken impression that mutations all result in major alterations of the phenotype, such as chondrodystrophic dwarfism, albinism, hemophilia, and galactosemia. We have learned, however, that these so-called visible mutations actually represent only a small part of the total of mutations that take place. Most mutations result in changes that are not so obvious, but that may affect viability and fertility. The different kinds of mutations are listed below in order of frequency of occurrence.

Neutral Mutations. These seem to outnumber all others and can be detected only by an analysis of the proteins they produce. The studies on human hemoglobin molecules revealed changes in the amino acids which had no detectable effect on the efficiency of the hemoglobin. So many of these changes were found that it was evident that such neutral mutations must be very common. Parts of a gene code areas of the polypeptide chain that are not vital to the

function of the protein. For instance, only a relatively small portion of an enzyme is required to mediate chemical changes. An alteration of an amino acid at this active site could have far-reaching effects, as we have learned, but an alteration at other parts of the molecule might have no effect at all on the efficiency of the enzyme. The same can be true for many structural proteins.

Neutral mutations might, at some future time when environmental conditions are different, have a value in evolutionary adaptation. Under changed conditions the altered gene might help a species survive. In a gene pool there might therefore be a storehouse of mutants that can make the organism more efficient than the original genes.

Detrimental Mutations. Many mutations have an effect on the organism expressing them, but the effect is small and not easily measured. Most such effects are detrimental, making the organism slightly less efficient; perhaps the liver does not remove toxic substances as well, the pancreas may be sluggish in responding to the homeostatic call for its secretions, or the kidneys may continue removing a mineral after it has reached its optimum concentration in the blood. None of these defects alone would be greatly harmful, but many such detrimental effects could greatly lower the efficiency of the body. All people carry some such genes, but when many are expressed in one person there is a cumulative effect that can be disabling, or even lethal.

Lethal Mutations. Many gene products are vital, and a mutation which alters an important part of such proteins can have an effect that is so extreme as to cause death. Lethal mutations are about twenty times more frequent than the better-known visible mutations. The time when the effect becomes lethal varies according to the stage of life at which the gene product is necessary for continued existence. One mutant gene might make defective microtubules of protein for the spindle figure. This would be a zygotic lethal, because the zygote would never be able to complete its first cleavage. A human mutation which causes a change at the active site of the enzyme needed for implantation would result in death at about the seventh day of fetal life because at this time the embryo must become implanted or it will be carried from the uterus. A mutation in a gene that produces a structural protein in the human heart muscles can cause death at about the third week because at this time the embryo becomes dependent on circulating

blood pumped by the heart for its continued existence. A mutant that fails to produce a normally functioning kidney would not be lethal during fetal life because the excretory wastes pass through the placenta into the mother's blood stream. At birth, however, kidney function is necessary and death comes within a few days if the kidneys do not function properly. The gene for Tay-Sachs disease causes a buildup of fatty materials around the nerves, but the afflicted child may live as long as five years before the effect becomes lethal. Other late-acting lethals can cause death even later in life.

Most lethals are recessive and each person probably carries an average of about four of these. Dominant lethals may appear, but are eliminated from the gene pool the first generation, with the rare exception of those that cause death after children may have been borne. A few intermediate lethals may have a nonlethal effect when heterozygous and cause death only when homozygous. In domestic poultry a mutant gene causes short, crooked legs when it is heterozygous. Chickens with this trait are known as creepers because they cannot walk upright. When two creepers are crossed they yield offspring in a ratio of one normal to two creepers. About one-fourth of the eggs do not hatch and when some of these are opened a dead embryo with great skeletal defects can be seen. These are the homozygotes.

A human intermediate lethal causes brachyphalangy when heterozygous. The fingers appear to have only two joints because the middle joint is greatly shortened and often fused to one of the other finger bones. The trait was thought to be a simple dominant one until two persons having it married. Of their four children, one was normal, two had the short fingers, but the fourth was born without any fingers or toes and had other skeletal defects which caused death shortly after birth. This is the ratio that would be expected from an intermediate lethal.

In many cases a lethal may kill too early to be detected and can be recognized only by the unusual ratios of the offspring and by a reduction of the total number of expected offspring. A typical example is the gene for dichaete wings in *Drosophila*. A fly heterozygous for this gene has wings spread out to the side instead of back over the body and also has short bristles on the thorax. A cross of two such flies yields 1 normal:2 dichaete. Such a ratio would be expected if the homozygotes for the gene died.

X-linked lethals are relatively easy to detect through tabulation of the sex ratio. In animals with the XY method, a recessive lethal carried by a female will cause death of half of her male offspring, resulting in a 2:1 female-male ratio. A dominant X-linked lethal mutant that appears in the reproductive cells of a male will result in death of all female offspring, but the male offspring will not be affected because they receive their single X from the female parent. If such a mutant appears in the female reproductive cells, however, half of both male and female offspring will die and the sex ratio will not be altered.

Visible Mutations. These are the best known because they can be recognized by observation, but perhaps no more than 1% of the total mutations fall into this category. Dominant visibles are easy to detect because they appear in the first generation after they have occurred. Most studies on the human mutation frequency have been done on dominant visible because we cannot conduct the necessary breeding tests to detect recessive visibles. A change in the amino acid sequence of a protein, if it has any effect at all, is likely to result in an inability to perform some function, and, as we have learned, such changes are most likely to be recessive.

Recessive visibles, therefore, are more common, but harder to detect in diploid organisms. Close inbreeding tends to bring out recessive mutants by increasing homozygosity. Also, special techniques have been devised to detect them in the first generation. Mice from a wild-type strain can be mated to some from a strain which is homozygous for many recessive genes. In most of the offspring only the wild-type phenotype will be observed, but should there be a mutation in the reproductive cells of a wild-type mouse which corresponds to one of the mutant recessives in its mate, the mutant phenotype will show in the first generation. Such a method can detect only those mutations that occur at specific loci, but it does give an indication of the total mutation rate.

FREQUENCY OF MUTATIONS

How often do genes mutate? If we consider one gene at a specific chromosome locus, the frequency of spontaneous mutations (those not induced by mutagenic agents) is very low. Hundreds of thousands of organisms must often be studied to get an accurate estimate of the frequency of mutations of this nature.

Drosophila. Lethal mutations in *Drosophila* are so much more common than visibles that they were studied first. Special techniques were devised which permitted detection of recessive lethals in two generations of breeding. The frequency was found to be slightly more than 1%. If we add to this figure the smaller number of visibles and the larger number of detrimentals and neutrals, the estimate of total mutations rises to about 5% per generation. This means that about one in each 20 gametes carries some sort of mutation which has arisen during that generation. This figure includes all loci on all chromosomes, so the rate for one locus would be much smaller. H. J. Muller estimated that any single gene has only about one chance in a million of undergoing mutation during its life span from one replication to another. In other words, a gene replicates itself perfectly in all cases except this one out of a million.

Genes vary considerably in their mutation frequency. The mutation of the wild-type allele to yellow body in *Drosophila* is about one in 9000 gametes, but the mutation of another gene to ebony body is only about one in 50,000 gametes.

Corn (Maize). L. J. Stadler, in his extensive studies of mutations in corn, planted seeds of the wild type in rows, but planted every fifth row with seeds from a stock that expressed many recessive mutant traits. The tassels were cut from the wild-type plants before they matured to assure that all fertilizations came from pollen of the mutant strain. Any mutation appearing in the ovules of the wild type that matched one of the mutations in the mutant type would be expressed. Only seed characteristics were observed, so the mutations could be recognized simply by looking at the seeds that grew on the ears of the wild-type plants. Some of the gene frequencies determined by this method are shown in table 15–1.

Microorganisms. Mutation frequency detection is relatively easy in microorganisms because they are haploid and enormous numbers can be grown in a short time. Resistance to an antibiotic is a good example of a mutation in bacteria. The wild-type strain of *Sarcina lutea* cannot grow on a medium containing even very small quantities of streptomycin. We can place millions of bacteria on a culture dish containing this antibiotic. A few of these may grow into colonies. These would represent mutations to streptomycin resistance. It appears as if the mutation confers the

TABLE 15–1
SPONTANEOUS MUTATION RATE IN DIFFERENT ORGANISMS

Organism	Mutation	Frequency per Million Generation Cycles
T₂ bacteriophage (virus)	Lysis inhibition	0.01
E. coli (bacterium)	Lactose fermentation	0.20
	Streptomycin resistance	0.04
	Tryptophan independence	6.00
Neurospora (mold)	Adenine requiring	0.04
Chlamydomonas (alga)	Streptomycin sensitivity	1.00
Maize (corn)	Red aleurone	11.00
	Sugary endosperm	2.00
	Shrunken seed	1.00
Human	Chondrodystrophic dwarfism	42.00
	Retinoblastoma—tumors on retina of eye (dom.)	23.00
	Aniridia—absence of iris of eye (dom.)	5.00
	Albinism (rec.)	28.00
	Hemophilia (X-linked rec.)	32.00

ability to produce an enzyme which can break down the antibiotic.
Figure 15–5 shows how mutations for defective enzyme production
can be detected in Neurospora.

It is even possible to obtain mutation rates for viruses. The T₂
phage that infects E. coli can be used to illustrate. The bacteria are
inoculated so heavily onto a culture dish that a milky growth
appears over the entire plate. Then a little of a culture containing
the phage is spread over the surface. After incubation, clear areas,
known as **plaques**, appear on the bacteria culture. Each plaque
is an area where a single phage particle has multiplied and caused
lysis of the bacteria in this region. Among many thousands of such
plaques a few may be seen that are distinctly larger than the others.
These represent a mutant strain that produces rapid lysis. Table
15–1 shows some of the mutation rates of different organisms.
Mutation frequencies in microorganisms are very low compared
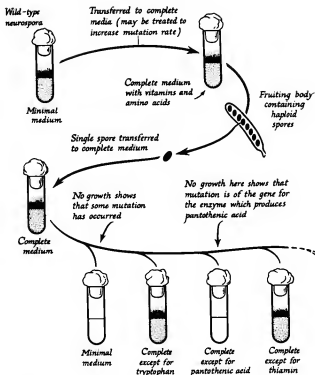
Fig. 15–5. Mutation detection in the mold Neurospora. By putting the mold on media lacking particular substances it is possible to determine which enzyme is lacking. (From Winchester, Genetics, 2d ed., Houghton Mifflin.)

to those in larger organisms, but we must remember that in many microorganisms there is only one gene replication per generation cycle. In large multicellular organizations there will be many gene replications and cell cycles for each generation, so mutations will have a chance to accumulate.

Humans. Dominant mutations in humans are easy to detect because anytime a child shows a trait not shown by at least one parent, a mutation must have occurred, provided the gene has 100% penetrance (see chapter 18). In Denmark careful records are kept of the appearance of such traits; from these records, estimates of mutation frequency can be made. For instance, 14 out of 127,763 babies born had chondrodystrophic dwarfism, a dom-

Fig. 15-6. Chondrodystrophic dwarf. This is a dominant trait and has been studied extensively to determine the mutation rate in man. When it appears in a child and neither parent shows it, a mutation has occurred. (Courtesy C. Nash Herndon.)

inant trait characterized by shortened arms and legs. Three of these had a parent with the trait, but the other eleven seemed to represent a mutation in the germ cells of one of their parents. The rate would be one in each 11,500 births or one in each 23,000 genes at this locus in the parents. Assuming an average generation cycle of thirty years, the rate of mutation of the normal allele to this dominant mutant form would be once in each 690,000 years.

Other human mutation rates are shown in table 15-1. Since these are the mutations most often observed, they must be among those genes that mutate most frequently.

SOMATIC MUTATIONS

So far we have concentrated our attention on mutations that appear in the reproductive cells and are transmitted to offspring. We must remember, however, that the same forces that bring about mutations in one kind of cell can cause them in all other types of cells. Many mutations probably do occur in somatic (body) cells,

Fig. 15–7. An albino area around the left eye of this man could be the result of a somatic mutation in one cell of the young embryo.

but in the mature organism they are generally never expressed. Those that occur in very early embryonic stages can, through cell division, be propagated until a sufficiently large mass of tissue is formed.

Plants. Somatic mutations can be expressed if they occur in the growing stems of plants. An entire branch of a tree may be formed from a single mutant cell and produce a different kind of fruit. The navel orange, the Delicious apple, and seedless grapes all arose from such mutations. They have been propagated by budding and grafting. Mutations that appear in the plant embryo may result in mosaic patterns of growth. The variegated leaves of some plants can be explained by such mutations.

Animals. Mutations in cells of young animal embryos can likewise result in mosaic patterns. Some fruit flies have been observed with a white pie-shaped section in a wild-type red eye. The gene for white is sex-linked, so the mutation could occur in a male or a heterozygous female early in embryonic development. Some people have a single albino area of the body. This could result from a

mutation in the early embryo of a person heterozygous for albinism. The normal allele could mutate to the one for albinism, so this small section of the body would contain cells homozygous for albinism. Occasionally a person is seen with one blue eye and one brown eye which might be due to an early somatic mutation.

Mutations that occur at later stages of life generally have no detectable effect. A small island of tissue with the mutation may develop, but it will probably not be noticeable. One important exception is a mutation that occurs in a gene involved in the correlation of cell growth. The result may be an uncontrolled, cancerous growth of the descendants of this cell. This is probably why agents which are mutagenic are generally also carcinogenic (cancer-causing).

PROBLEMS

1. A farmer finds a tom turkey in his flock that has a much broader breast than the others. How could he determine if this resulted from a mutation or if it were merely an environmentally induced freak? If it proved to be due to a recessive mutation, how could he establish a pure-breeding flock of such turkeys?

2. Since neutral mutations have no phenotypic effect, how do we know that they occur?

3. Some alterations of the base pairs in genes do not alter the polypeptide chains which the genes code. Explain.

4. Why are reverse mutations generally less frequent than direct mutations?

5. Lethal mutations are more frequent than visible mutations. Give a possible reason for this.

6. Bacteria show a mutation rate much lower than that of humans. Does this mean that the genes of bacteria mutate less frequently? Explain.

7. A mutation in the virus which causes influenza has resulted in a worldwide epidemic of this disease. What could be the nature of the mutation which would make the organism more virulent?

8. Genetic studies indicate that cancer is caused by genetic changes within somatic cells, yet other studies indicate that certain chemicals, such as the tars in tobacco smoke, cause cancer. How can you correlate these two findings?

16. INDUCED GENETIC CHANGES

Various environmental agents are capable of inducing mutations and chromosome aberrations. Many of these agents have been created by humans in relatively recent times. Plant and animal breeders welcome such agents as ways to speed up the process of genetic change. Selection for desirable cultivated plants and domestic animals is more effective with an increased variety of inherited characteristics. Breeders often are not concerned about the fact that most genetic changes are harmful. They can discard the great majority of offspring that show harmful alterations and save the very few that happen to be desirable. No such selection is possible with human beings, however, since we do our best to save all who are born. Hence there is concern over the possible future effects of human exposure to excessive quantities of mutagenic agents. In this chapter we shall first discuss the kinds of mutagenic agents and how they bring about genetic changes. Then we shall try to evaluate the impact of these genetic alterations on future generations.

KINDS OF MUTAGENIC AGENTS

The main types of mutagenic agents are high-energy radiation (x-rays and radioactive isotopes), ultraviolet light, and certain chemicals and drugs.

High-Energy Radiation. Before 1895 people had no knowledge of high-energy radiation. In that year, however, Conrad Roentgen devised a vacuum tube through which he passed a high-voltage direct current of electricity. As the current jumped a gap it emitted strange rays, which he called x-rays (x for unknown). These rays could not be seen, yet they caused fluorescence of certain chemicals and they exposed photographic emulsions. Furthermore, they were of such high energy that they could penetrate

solid objects and be absorbed by some substances. This feature made it possible to make photographs that would show the interior of the human body. The denser body structures absorb proportionately more rays than the less dense organs—resulting in a shadow image on photographic film. Also, by placing a screen containing fluorescent minerals behind a person, a visual image was formed by means of which the living organs could be viewed in their activities. Roentgen's discovery had great medical value, but harmful effects were soon noted. Many persons working with x-rays held their patients with their hands during exposure. Extensive exposure to the rays had a cumulative effect and cancerous growths developed on the hands. Many of these doctors had to have their hands amputated as deterioration continued. Many even lost their lives because of overexposure.

In 1927 H. J. Muller discovered that x-rays induced mutations in *Drosophila*. Heavy doses of such radiation were found to greatly increase the number of mutations. It was also shown soon after that x-rays increased the number of chromosome aberrations.

In 1896 Becquerel found that certain chemical substances, such as uranium ore, also gave off high-energy radiation similar to that generated in an x-ray tube. A mass of uranium ore contained a certain small number of unstable isotopes whose subatomic particles emitted high-energy radiation as they attained stability. Soon Marie and Pierre Curie isolated radium from uranium ore, and for many years this was used to treat cancer, since cancer cells were very susceptible to damage from such radiation. Later many other radioactive isotopes of atoms were discovered.

In 1945 another great source of radiation was made available. It was shown that man learned how to split the uranium atom with a great release of energy in the form of heat, light, and high-energy radiation. Many radioactive isotopes also were created as a result of the fission. When the atomic bomb was developed through the application of atomic fission, atmospheric explosions spread radioactive isotopes all over the world. Hydrogen fusion bombs were then developed and they had even greater power and generated even more isotopes. Controlled fission of the atom has become possible and is being used in nuclear generating plants to help supply our growing need for electricity. However, safe disposal of radioactive wastes generated in the process is a major problem that has restricted the use of these plants.

Ultraviolet light, like x-rays, is radiation of short wavelengths, but it has a very low penetrating power because it lacks the energy of the much shorter wavelength gamma rays of the x-ray tube and radioactive isotopes. Because bacteria are very small, however, ultraviolet rays can penetrate them easily and have on them a highly mutagenic effect. L. J. Stadler found that ultraviolet rays also caused mutations in corn pollen grains if the nucleus which fertilized the ovule lay near the top of the pollen grain. Edgar Altenburg even found a significant increase in mutations in exposed *Drosophila,* but he had to flatten newborn males between quartz glass and expose them so the rays would reach the nuclei of the cells of the testes. (The newborn flies are so soft that very survived this extreme flattening.)

Mutagenic Chemicals. In 1930 Rapaport in the Soviet Union reported an increased mutation rate after treatment of certain molds with nitrous acid. This was confirmed in 1939 by Thom and Steinberg in the mold *Aspergillus.* Then in 1956 Charlotte Auerbach reported a fiftyfold increase in X-linked mutations in *Drosophila* as a result of treatment with mustard gas, the poisonous gas used in World War I. The list of mutagenic chemicals has since been expanded to include formaldehyde, ethyl urethane, acridine dyes, epoxides, phenol, manganous chloride, bromouracil, dioxan, and even caffein and theobromine which are so widely consumed in coffee, tea, and chocolate. Many of the results have been obtained by tests on bacteria, molds, and tissue cultures of higher animals, so we cannot conclude that these compounds are necessarily mutagenic in living higher organisms. They are certainly under suspicion, however, and caution should be exercised in their use.

Drugs. LSD has been found to increase the number of chromosome aberrations when applied to human tissue culture cells. Some reports also indicate a significant increase in such aberrations in the lymphocytes of persons who have used the drug extensively, although other studies have not been conclusive in this regard.

METHOD OF MUTATION INDUCTION

When the mutagenic effects of x-rays were discovered it was first assumed that a quantum of radiation made a "direct hit" on a

particular part of the gene that somehow knocked the gene parts out of their normal order. With the discovery of chemical mutagens and findings that showed the effect of oxygen and temperature, the reasoning has swung to a chemical explanation.

Ionizing Effect of Radiation. High-energy radiation induces ionization in matter. In fact, the original measure of radiation, the **roentgen,** was based on the amount of ionization induced in a certain volume of gas. The energy of the radiation may force an electron out of its orbit, thus changing the atom into a positive ion. The negative electron then may be captured by a nearby atom, which then becomes a negative ion. Ions tend to combine with oxygen, thus creating chemicals that can interfere with the proper arrangement of bases within a gene during critical stages of replication. This fact was discovered when it was found that bacteria and *Drosophila* showed far less mutations if they were kept in a very low oxygen environment at the time of radiation. Temperature was also found to be a factor. *Drosophila* raised at a temperature of 27°C had about 2.5 times the number of mutations of those raised at 17°C. Tadpoles radiated at a very low temperature survived a dosage which would have been fatal at higher temperatures. Since chemical reactions are slowed at low temperatures, this evidence supports the idea of chemical production of mutations induced by radiation.

Genetic Engineering. Much has appeared in the popular press about the potentialities of genetic engineering as a means of changing harmful genes to normal ones. If such were possible we would not have to worry about the induction of harmful genetic mutations because the engineers could reverse our harmful genetic changes. The type of mutation induced was found to depend on the chemical agent used. Also, different organisms respond differently to mutagenic chemicals. Hydrogen peroxide causes mutations in *Neurospora*, but not in higher plants. Urethane and phenol are mutagenic in *Drosophila* and in higher plants, but not in *Neurospora*. Westergaard found that in *Neurospora*, bromoethyl methane sulfonate caused mutations of the gene ad^- to ad^+ but practically no mutations of $inos^-$ to $inos^+$. Ethyl methane sulfonate, however, caused mutations of both genes. Mutations induced in *Drosophila* by mustard gas are in a different proportion to those induced by high-energy radiation. It is hoped that chemicals will be discovered that will bring about desirable changes of specific genes without affecting

others. Geneticists must greatly extend their discoveries, however, before there is any chance for realization of this goal.

INDUCED CHROMOSOME ABERRATIONS

Agents that induce gene mutations also usually cause chromosome aberrations. Mutations, however, tend to occur in a linear relationship to dose, whereas chromosome aberrations show an increasing frequency with increasing dosage. Lasting aberrations are more likely to be produced when two chromosome breaks occur in the same cell at about the same time. (See chapter 13.) Mutagenic agents also increase the chance for nondisjunction of chromosomes, with resultant trisomy and monosomy.

Results of Somatic Aberrations. Chromosome aberrations that occur in mature somatic tissue are much less damaging than those appearing in rapidly growing tissue. Mature human brain cells, for instance, will never undergo division again and are very resistant to damage from high-energy radiation. Even though an aberration may be induced, the genes are still in the same proportion as before and generally continue to function as they did. An aberration induced in growing and dividing cells, however, is likely to show somatic effects because daughter cells may receive unbalanced genetic constitutions. Such cells in humans are the blood-forming cells in the bone marrow, the epithelial cells of the skin and lining of the digestive tract, the hair roots, and the reproductive cells. A man who receives a relatively high exposure to high-energy radiation may lose his hair, develop ulcers on the skin and intestine, become anemic because of reduced red blood cells, become leukopenic because of reduced white cells, bleed excessively because of reduced blood platelets, and may become sterile because of damage to the sperm-producing cells. His bones, muscles, brain, kidneys, liver, and lungs, however, may show little damage because they do not contain rapidly growing and dividing cells. Cancers and leukemia may also appear because of genetic changes in the rapidly growing tissues. Fortunately, cancer cells are also very susceptible to radiation damage because they are so rapidly growing. In fact, they can be killed with a dose that does not kill the more slowly growing normal surrounding tissues. It is strange that radiation which can induce cancer is also a powerful weapon in destroying cancerous tissue.

Fig. 16–1. Radiation damage to a monkey's head. The head received about 2000 rads of gamma rays from cobalt 60. The hair and teeth have fallen out and the nose and ears are deteriorating. (Courtesy A. J. Riopelle.)

Influence of Age. Age is an important factor in radiation damage. Younger animals have cells that are growing at a faster rate than those of adult animals, so they are more susceptible to damage. Newborn rats will be killed with a dosage of about 600 R, but adult rats require about 750 R. The embryo is most sensitive of all; a dose of only 200 R will kill all the embryos in a female rat that is eight days pregnant. This fact was demonstrated in Hiroshima when women, exposed to the radiation from the atom bomb, aborted the fetuses they were carrying. Although the women suffered only radiation sickness, their more susceptible embryos were killed by the exposure.

Results of Aberrations in Reproductive Cells. Aberrations induced in reproductive cells are frequently lethal to the cells. This accounts for the sterility that develops after extensive radiation. Most of the early workers with x-rays had no more children even though they showed no other signs of radiation damage. The abnormal distribution of chromosomes during meiosis which follows such aberrations results in death of most of the gametes in both sexes. However, such sterility may be temporary. The germinal epithelium may contain some cells that are not damaged and in

time these may repopulate the area with sufficient cells to cause a return of fertility. Some survivors of the Hiroshima bomb blast had no children for several years, but then became fertile again. In doses short of those causing complete sterility, there may be an increase in abortions and abnormal babies as a result of induced aberrations. Unlike the majority of mutations, these abnormalities usually appear in the first generation.

Radiation Tolerance Doses. Species vary greatly in their susceptibility to radiation damage. Generally, the smaller and less complex organisms are more resistant. The toleration to whole-body radiation is often expressed in terms of LD50 (that is, the amount of radiation required to kill half of the exposed individuals). The LD50 figure for humans is about 450 R, while that for rats is about 700 R. The dose for a salamander increases to about 3000 R, for yeasts to about 30,000 R, and for *Drosophila* to

Fig. 16–2. Human chromosome aberrations induced by radiation. This cell is from a tissue culture exposed to 50 rads of x-rays. Three aberrations can be seen: D—deletion, T—translocation, and I—isochromosome formation.

46,000 R. Plants, as a whole, are more resistant than animals. Barley seeds will still germinate after an exposure to as much as 50,000 R. It has been said that should we be so stupid as to spread sufficient radioactive fallout over the earth to kill all human life (and we now have that capability), we would leave the world to the plants, insects, bacteria, and other lower forms of life.

Within a species there is also considerable variation to radiation damage. General health and vitality play a part. Individuals that are already weak will be killed by a lower exposure than those who are strong, but heredity is also a factor. Although the LD50 for humans is about 450 R, some will be killed by an overall body exposure as low as 250 R, but 600 R is required to kill all exposed persons. The influence of heredity is clearly demonstrated in mice. One strain, BALB, has an LD50 of 500 R, but another strain, C57BL, has an LD50 of 630 R. When these two strains are crossed, the hybrids have an LD50 about halfway between these two figures.

HAZARDS OF INDUCED GENETIC CHANGES IN HUMANS

Mutations and chromosome aberrations occur spontaneously at a certain low rate. During this century, however, humankind is being exposed to mutagenic agents that can increase the number of these genetic changes. The important question is, what effect will these induced alterations have on the generations of the future? Most of the concern is about the damage to the people on earth today. As a result of the increased exposure to radiation, for instance, how many extra cases of leukemia, cataract, cancer, shortened life spans, and abortions will we have? A significant increase in all of these maladies has been detected to those exposed to the radiation from the bomb in Hiroshima. When we evaluate the effect of the increased radiation we will receive because of the wastes from nuclear fuels and weapons that are released into the air, water, and soil, we talk in terms of health hazards to the people of today. Yet, some geneticists estimate that the damage to those of the future will be greater than to those now living. A mutation induced today might be carried in the recessive state for many generations, multiplying in number with each generation, and

eventually causing deaths and deformities when it becomes homozygous in distant descendants.

Studies on induced mutations in experimental animals and plants indicate that the mutation rate is in proportion to dose, a linear relationship. The kinds of mutations are the same—they are no more severe when they arise from heavy radiation than when induced by smaller doses—but more mutations occur after the heavy dose.

It is difficult to study the effect of very low levels of radiation because the number of mutations induced will be only slightly higher than those that occur spontaneously. It is important, however, for us to know if there is a threshold below which no mutations are induced. Extensive studies on *Drosophila* and mice indicate that there is no such threshold, that some mutations are induced all the way down to practically zero extra exposure, although the proportion may be smaller at very low levels.

Some might question the extrapolation of the results from fruit flies and mice to humans. How can we know that we will be similarly affected? For one thing, genetic material is the same for all organisms and it stands to reason that it will be affected the same in all species. Second, we have positive results from studies of the human sex ratio. Raymond Turpin, at the University of Paris, found a reduced percentage of males born to women who had received extensive x-ray exposure in the region of the gonads. The percentage of males born to women before exposure was 54.4, but the children born to these women after exposure included only 47.1% males. The change is apparently the result of the induction of recessive lethal mutations on the X chromosome of the women. Such mutations would result in the early death of male offspring who might receive such an X, but would not injure female offspring who would receive another X from their fathers which would, in all probability, contain the dominant normal allele of the lethal mutants. Over 4000 persons were included in this study and the amount of radiation involved was between about 70 and 270 R. Since the X chromosomes of a woman are only one pair of a total of twenty-three, these results would indicate X-linked recessive lethals only.

Studies of the children born to residents of Hiroshima and Nagasaki at the time of the bomb explosions have failed to show definitive differences in abnormalities and male sex ratio when com-

pared to children born to residents of other cities of Japan. The average amount of radiation received by the Hiroshima residents, however, was much less than that received by the subjects of the Paris studies and, with the numbers involved, it would not be possible to detect a significant difference in mutation rate.

PROBLEMS

1. The discovery that high-energy radiation would increase the mutation rate was hailed as a great boon to plant and animal breeding, but was a cause of great concern as to its impact on humans. Explain.

2. Ultraviolet light is highly mutagenic in bacteria, yet we are little concerned about this effect in humans. Explain.

3. Agents that are carcinogenic (cancer causing) are also likely to be teratogenic and mutagenic. Why should these effects be correlated?

4. How did the discovery that oxygen concentration was related to induced mutations support the concept that radiation induces chemical changes within the cell which then can cause mutations?

5. The number of mutations induced seems to be in direct relation to the amount of radiation received, yet the proportion of permanent chromosome aberrations is greater with heavy exposure than with low exposure.

6. Why are embryos so much more sensitive to radiation damage than adults?

7. Most mutations are recessive, yet a few are dominant. Some studies have been made on the sex ratio of children born to men who have been exposed to heavy radiation. What effect would X-linked dominant lethals have on the sex ratio of the children of these men?

8. Advocates of atmospheric nuclear bomb testing have argued that the amount of radiation that would spread around the world would be too small to be significant. In the light of what you have learned in this chapter, evaluate the validity of this argument.

17. POPULATION GENETICS

Much of our study up to this point has been concerned with genes in individuals, the effect of genotypes on phenotypes, and the ratio of particular phenotypes in offspring. Population genetics, however, is concerned with the **gene pool** of an entire population. A population is a group of freely interbreeding individuals within a restricted area.

The exact distribution of genes within a population is dependent on the types of matings that occur.

MATINGS WITHIN POPULATIONS

Random Mating. Within a wild animal population an individual possessing a particular trait may be no more nor less likely to mate with another showing the same trait than chance would dictate; therefore mating is random. The so-called black bear population of Yellowstone Park exists in three color phases. About 75% are black, about 20% are brown, and about 5% are cinnamon colored. A male with a brown coat does not seem to be particular about the color of the coat of a female he mates with. He will probably mate with the first receptive female he comes in contact with, provided he is not chased away by a stronger male. Hence, his chance of mating with another brown bear would be about 20%, the same as the frequency of brown bears in the population. With random mating the three color phases tend to remain in equilibrium and the same number of each color is produced each generation.

In wild plants, crossing is random. The pollen grains from one plant will land on the stigmas of any other plant of the same species, regardless of its individual characteristics. Hence, certain

traits, such as colors of wild flowers, tend to remain in about the same proportion year after year.

Assortive Mating. Assortive mating occurs when organisms with similar traits tend to mate with one another more often than chance would dictate. If brown bears preferred other brown bears and black preferred black, their mating would be assortive. Assortive mating seldom occurs in wild populations, but is quite common, because of human intervention, in domestic animals and cultivated plants. Dog breeders are careful to allow matings only within a breed so as to keep it pure. Hence the genes within the dog population tend to be grouped together in a number of separate gene pools. The same is true of cultivated plants. A plant breeder artificially spreads the pollen so as to maintain varieties in the pure state.

Preferential Mating. This occurs when a particular type of individual mates more often than other members of the population. A male animal with the strength and aggressiveness to fight off other males will mate with many females. In domestic animals a fine specimen may be mated repeatedly so as to get as many offspring as possible with the desirable genetic qualities. By artificial insemination, a fine bull may sire hundreds of calves while less desirable bulls may leave no descendants. It is through such matings that we have been able to alter the gene pool of domestic animals and cultivated plants in order to better serve our needs. In nature, preferential mating is the basis for natural selection whereby species are improved.

Matings in Human Populations. All these types of matings occur in human populations. Matings appear to be random with respect to blood types and other traits involving antigens and physiological reactions that do not have obvious phenotypic effects. (People are not likely to check each other's blood type before considering marriage.) When the traits affect physical features that are clearly defined, however, matings are sometimes assortive. This is true with respect to the density of melanin deposits in the skin. A person with the darker pigmentation characteristic of those with African ancestry is much more likely to choose a mate with similar pigmentation than chance would indicate if mating were random. The Jews of America are much more likely to marry those of their own background than those of other groups. The same is true of American Indians, Italians, Mexicans, and so on. Such assortive

mating tends to maintain racial and ethnic groups within a population, although in the course of time it breaks down and the genes become more evenly distributed.

Assortive mating in human populations involves other characteristics than racial or ethnic ones, however. A man of short stature tends to seek a mate who is also well under the average height, although there are notable exceptions. Handicapped persons often marry others with similar handicaps. A person is likely to feel more comfortable with one who shares some of the same characteristics.

Preferential mating also occurs in humans. When a particular trait is greatly admired by all, any person with that trait is likely to have more than his or her share of offspring. Albinism exists in

Fig. 17–1. An albino Cuna Indian girl from Panama. The incidence of albinism is high in this population, possibly because of sexual selection. This form of albinism results from improper absorption of tyrosine so there is a little melanin in the hair and skin but much less than in others in the population.

all races, but is unusually prevalent among the Cuna Indians of Panama, who consider it particularly attractive. Among these Indians an albino man will have many girl friends and sire a great many children. Likewise, an albino woman will be the object of much male attention and will probably bear more children than other women. Even in monogamous societies preferential matings may play a part. A woman with the preferred traits will be more likely to marry early and have more children than women who lack the traits. A man having such traits will probably father more children than others.

THE HARDY-WEINBERG PRINCIPLE

Population geneticists use mathematical methods to determine gene frequencies and to predict the appearance of specific traits in the populations. One of the most useful of the mathematical tools is known as the Hardy-Weinberg principle. This formula was developed in 1908 by an English mathematician, G. H. Hardy, and a German physician, Wilhelm Weinberg. Basically, it holds that in any stable and randomly breeding population the genes are in equilibrium, and the frequency of any gene in the population can be determined by observing the percentage of those who express the trait.

Determining Gene Frequency. Suppose we survey a representative sample of the people on an island off the coast of Portugal and find that 16% of them have blue eyes (unpigmented iris). With this information we can determine the frequency of the gene for blue in the population, the frequency of the allelic gene for brown (pigmented) eyes, the frequency of heterozygous brown-eyed persons in the population, and the frequency of homozygous brown-eyed persons. This trait is a good one to use to illustrate gene frequency because the color of eyes would not be likely to lead to assortive mating and it has no advantage or disadvantage for survival.

We allow p to represent the frequency of the gene B for brown and q to represent the frequency of the recessive allele b for blue and employ the binomial $(p + q)^2$ to determine the frequencies of each of the two alleles. We know the frequency of q^2; it is the percentage of people with blue eyes, 16% (they are homozygous for the recessive gene). By taking the square root of q^2 we obtain

the value of q. This is 40%, the frequency of the gene for blue in the population. Since the genes that are not b are B, the frequency of B is 60%. This is the value of p, and we need only to square this figure to get the number of homozygous brown-eyed persons in the population, 36%. The rest of the brown-eyed persons would be heterozygous, with a frequency of 48%. We can expand the binomial and summarize this as follows:

$p^2 + 2pq + q^2 = 1.00$

$q^2 = 0.16$ (known) so $q = \sqrt{0.16} = 0.40$ (frequency of gene b)

$p = 1.00 - 0.40 = 0.60$ (frequency of gene B)

$p^2 = 0.60^2 = 0.36$ (frequency of homozygous brown, BB)

$2pq = 2 \times 0.60 \times 0.40 = 0.48$ (frequency of heterozygous brown, Bb) or $1.00 - (0.16 + 0.36) = 0.48$ (frequency of heterozygous brown, Bb)

The distribution can be represented by a Punnett square:

	p (0.60)	q (0.40)
p (0.60)	p^2 0.36	pq 0.24
q (0.40)	pq 0.24	q^2 0.16 (known)

Gene Equilibrium. If one looks at the 3:1 ratio in the second generation of a cross between a homozygous recessive and a homozygous dominant, it may appear as if the recessive trait will appear less frequently each generation. Actually, if a recessive trait has no selective advantage or disadvantage, it will remain constant in frequency through the generations. We can use the example of blue and brown eyes to demonstrate this. The kinds of matings and their frequency that would produce blue-eyed children would be:

Marriages	Children	Proportion of Blue-eyed Children	
$bb \times bb$	= all blue	0.16×0.16	= 0.0256
$bb \times bB$	= one-half blue	$0.16 \times 0.48 \times 0.5$	= 0.0384
$Bb \times bb$	= one-half blue	$0.48 \times 0.16 \times 0.5$	= 0.0384
$Bb \times Bb$	= one-fourth blue	$0.48 \times 0.48 \times 0.25$	= 0.0576
	Total blue-eyed children		= 0.1600

The number of blue-eyed children will therefore be the same in the offspring as it was in the parents, and this will hold true throughout succeeding generations. Later in this chapter we shall see how the frequency of a gene can change when certain forces are operating.

Genes of Lesser Frequency. When a recessive trait is relatively rare, percentages will involve many decimals and it is usually more convenient to use fractions. Consider the following example. About one person in each 10,000 born in the United States has *cutis laxis*, skin which stretches greatly and returns to its normal position slowly. This is only 0.01% of the population, or 0.0001. It is simpler to use 1/10,000 as the frequency of the trait. The gene frequencies and phenotypes would be as follows:

$q^2 = 1/10,000$ so $q = \sqrt{1/10,000} = 1/100$ (frequency of gene c)

$100/100 - 1/100 = 99/100$ (frequency of allele C)

$(99/100)^2 = 9801/10,000$ (frequency of homozygous normal CC)

$2 \times 99/100 \times 1/100 = 198/10,000$ (frequency of heterozygous Cc)

SELECTION AGAINST RECESSIVE TRAITS

When a recessive phenotype is harmful or less efficient than the dominant alternate, natural selection tends to reduce the number of genes for this phenotype in the population. Similarly, artificial selection can reduce recessive genes for traits considered undesirable in domestic animals and cultivated plants. The effectiveness of selection can be predicted by mathematical means.

Artificial Selection. A breeder of Wyandotte chickens has a flock in which 75% have the dominant rose comb (a multiheaded comb) and 25% have a single comb. He wants only rose-combed chickens and initiates a program of selection against single comb. No single-combed chickens are allowed to breed. The chickens with the single comb are homozygous (ss) and, by the Hardy-Weinberg principle, we find the gene frequency of s to be 50%; $\sqrt{0.25} = 0.50$. Since single comb does not restrict the viability or reproductive capacity, this gene frequency would remain constant if

there were no selection against it. The distribution of genotypes in this flock would be ¼ SS:½ Ss:¼ ss. The breeder eliminates the last group, so the breeding population becomes ⅓ SS:⅔ Ss. By simply counting the letters we see that 66.6% of the genes are S and 33.3% are s. Hence, in the first generation after complete selection against single comb we would expect 11% with single comb.

$$s = 0.333 \quad \text{so} \quad ss = (0.333)^2 = \text{about } 11\%$$

Complete selection against the recessive phenotype for one generation has reduced the number of these phenotypes by more than half. The efficiency of selection decreases, however, as the number of recessive phenotypes becomes less. A simple equation can be used to determine the numbers of single-combed chickens in each generation:

$$qn = \frac{q_0}{1 + nq_0}$$

in which q = frequency of recessive allele; n = number of generations; q_0 = initial frequency of recessive allele, in this case 0.50; and q_1, q_2, q_3, and so on = frequency of recessive allele in first, second, third, and so on, generations.

To calculate the frequency for the first generation we get

$$q_1 = \frac{q_0}{1 + 1q_0} = \frac{0.50}{1 + 1 \times 0.50} = 0.333 \text{ or } 33.3\%$$

$$ss = (0.333)^2 = 0.11$$

After five generations we would obtain

$$q_5 = \frac{0.50}{1 + 5 \times 0.50} = 0.143 \text{ frequency of } s \text{ in population}$$

$ss = (0.143)^2 = 0.02$ or 2% of chickens with single comb

The breeder might feel greatly encouraged by the rapid reduction in the numbers of chickens hatched with single comb and continues his selection for another five generations. The results for a total of ten generations would be

$$q_{10} = \frac{0.50}{1 + 10 \times .50} = 0.0833$$

$$ss = (0.0833)^2 = 0.0069 \text{ or } 0.69\%$$

It is apparent that the efficiency of selection diminishes as the frequency of the trait is reduced. More and more of the recessive genes are carried by heterozygous individuals. For the first five generations the number with the recessive trait was reduced from 25% to 2%, which is 8% of the original or a 92% reduction. For the next five generations, however, the percentage went from 2% to 0.69%, which is only about a 66% reduction. Another five generations of selection would drop the percentage to 0.35%, which is only about a 50% reduction. Still another five generations (or a total of twenty generations) of selection would give only a 40% reduction. The breeder may begin to wonder at this point if he can ever completely eliminate the gene for single comb by this method.

Incomplete Selection. Selection may not always be complete. In natural selection particularly the individuals showing an undesirable recessive trait may only be partially hindered from reproducing. We can make allowance for this incomplete selection, however, by introducing the letter k, for **coefficient of selection,** into our equation, which would then be

$$q_n = \frac{q_0}{1 + knq_0}$$

If the individuals who express the trait produce only half as many offspring as those who do not express it, then k would have a value of 0.5. If we started with a gene frequency of 50%, then one generation of this reduced selection would be

$$q_1 = \frac{0.50}{1 + 0.5 \times 1 \times 0.5} = 0.40$$

Trait frequency $= (0.40)^2 = 0.16$ or 16%

The frequency of the recessive trait drops from 25% to only 16% as compared to a drop to 11% when there was 100% selection against the trait. After five generations the drop with a k factor of 0.5 would be to 4.9% compared to 2% when there is complete selection. Even though the selection is slower, it will effectively reduce the frequency of the harmful trait.

Gene Equilibrium. It might appear as if selection would gradually eliminate all harmful recessive traits, but as the traits become less common, an equilibrium is reached and the number of the genes in the population remains constant. The input of the

harmful genes by mutation balances their outgo, or elimination, by **genetic death.** (Genetic death may result from sterility, the death of an individual before time for reproduction, or any other factor which prevents the transmission of genes to future generations.) An alteration of either the input or the elimination, however, can affect the frequency of the genes in the pool.

Unfortunately, social and scientific advances of the present century may lead to a significant rise in the frequency of harmful genes. We are now being exposed to mutagenic agents, which can increase the number of harmful mutations. At the same time, modern sanitation, medical practices, and preventive measures are saving many who would have had a genetic death in the past. For example, each time a child with a certain enzyme deficiency is saved from death by a controlled diet, we give her a chance to pass on genes that otherwise would have been purged from the gene pool.

The combination of increased input of harmful genes and a decreased outgo can result in an ever-increasing number of such genes in the gene pool, with a consequent increase in the number of harmful genetic traits. It has been suggested that we substitute human selection for natural selection. Those who express harmful traits might be advised against having children. Even those who have been found to be heterozygous for harmful recessive genes might wish to refrain from parenthood. Also, we certainly should keep exposure to mutagenic agents to a minimum.

GENE VARIATIONS IN HUMAN POPULATIONS

Casual observation shows that gene frequencies may vary among different populations of the same species. Varieties within a species of frogs, snakes, birds, or other wild animals are apparent when they are observed in different locations. Charles Darwin observed such population differences among the finches on the Galapagos islands. Human races are also good examples of the variations that can exist in the gene pool of different populations of the same species. A native of Japan is easily distinguished from a native of Nigeria because the external physical features are clearly different. In addition, there are many genotypic differences that can be revealed only by immunological and physiological tests. Let us

tabulate some of the factors that have brought about these differences.

Natural Selection. Humans have spread from their point of origin, probably in central Africa, to practically all regions of the earth. The environmental conditions under which they lived have been quite varied, and natural selection has favored genes in some regions which have not been favored in others. It is no accident that persons who lived in open areas near the tropics have heavy deposits of melanin in the skin. Not only are they better protected from burning by the sun's rays, but they are less likely to produce an overabundance of vitamin D. This vitamin is produced in the skin when it is struck by sunlight, but both too much and too little of this vitamin can be harmful. Melanin filters the sun's rays, allowing less exposure of the deeper skin tissues where the vitamin is manufactured. In those living far from the equator, a fair skin with less melanin permits a better penetration of the weaker sun's rays during winter, and in summer it develops a tan that will prevent too much penetration. Inhabitants of tropical rain forests also tend to have less melanin because they are in the shade of trees most of the time. Selection has favored those with just the right amount of melanin for a particular environment.

We have learned that there may be times when selection favors harmful genes because the heterozygote has a survival advantage. The prevalence of the gene for sickle-cell anemia in persons having an ancestry from regions of heavy infestations of malaria, such as central Africa, is a good example. Heterozygotes for the recessive sickle-cell trait tend to survive malaria. The incidence of cystic fibrosis was found to be about 24 times more prevalent among the Caucasians living in Hawaii than among the native Hawaiians. The frequency of babies born with spina bifida, a spinal deformity, is about 20.5 times greater in England than in Japan. Such great variation in the frequency of harmful genes in different populations suggests that individuals heterozygous for such genes may have had an advantage over those who were homozygous for the normal alleles.

Sexual Selection. There are many clearly distinguished features of the face and body build that are characteristic of different human populations but do not seem to have any survival value. Some of these, at least, might be explained by sexual selection. Ideals of sexual desirability may vary greatly in different groups. In one

population a very long nose might be considered the height of feminine beauty or masculine attractiveness, and those with the longer noses would probably have an advantage in matings. In another population a short nose might be the desirable type. Albinism in the Cuna Indians was used earlier in this chapter to illustrate this point.

Male combat over the possession of females has played a part in selection in many species. The strength of a man in overpowering a reluctant female has no doubt been a factor also in primitive societies. In some populations it has been not strength, but a man's shrewdness in accumulating sufficient wealth to buy many women for his harem which has been a factor in selection.

Genetic Drift. Genetic drift is the term given to random fluctuations in gene frequencies. In large populations, such chance fluctuations level out and the Hardy-Weinberg equilibrium is not disturbed. However, in small populations in which the number of matings is small, gene frequencies may "drift." In time, one allele of a given gene pair might become more frequent by chance alone, not by selection. The other allele would then be less frequent, even if it had more potential adaptive value.

Genetic drift may also be at work in the evolution of new populations when a small number of members of a species migrates to a new, isolated area. In the case of human populations, this type of genetic drift is sometimes called the **founder principle.**

If colonizers, or founders, are a rather small group they are not likely to constitute a representative sample of the gene pool of the population from which they came. Hence the population descending from these founders might be quite different from the population from which they came. About 1500 years ago a small group of Tahitians set out in long canoes and traveled over 2000 miles of open water to the North Island of New Zealand. Their descendants are the Maoris who now live on this island. This small migrating group were not representative of the gene pool of the Tahitians, so the Maoris show distinct differences from the Tahitians, such as having a much lower frequency of type A blood and a much higher frequency of type B. Genetic drift could be one factor to account for this.

A study by Bentley Glass of a religious group known as the Dunkers in Pennsylvania showed the possible effect of genetic drift. A group of 28 of these people came from the Rhineland

region of Germany in 1719. Later they were joined by a few more, but they have remained isolated from their neighbors since then. The percentage of their blood types as compared to those of the Rhineland Germans and Pennsylvanians today is

Blood Types	O	A	B	AB
Dunkers	35.5	59.3	3.1	2.2
Rhineland Germans	40.7	44.6	10.0	4.7
Pennsylvanians	45.2	39.5	11.2	4.2

The difference in the proportion of A and B indicates that the founders were probably not representative of the German population from which they came. It is also possible that after arrival those who were type B, by chance, had more children than those of type A.

A catastrophe that wipes out most of a population and leaves only a few survivors can also result in genetic drift; the survivors might not have the same proportion of genes as were present in the population. A good example of this was found by Newton Morton on the island of Pingelap, one of the Micronesian islands of the South Pacific. About 6% of the people living there today have **achromatophobia**, a recessive trait characterized by total color blindness and extreme sensitivity to light. Only a fraction of 1% of the natives of other islands of this group have this trait. The explanation seems to lie in a hurricane which struck Pingelap in 1900, leaving only 20 survivors on the island. These 20 must have had a high proportion of the gene for this trait. Since they could not stand light, perhaps those having the eye defect were in caves or protected areas when the hurricane struck.

Differential Mutation. Some genes, such as the blood antigens, mutate very rarely. In regions where they occur they become established by selection, while they never occur in other regions and so are not present. Evidence seems to indicate that human blood was all type O in the early days of human existence on the earth. Then, perhaps in western Europe, a mutation resulted in the production of antigen A. This mutation spread over most of the earth in the thousands of succeeding generations, but still has its highest concentration around its point of origin. Another mutation,

which produces the B antigen, seems to have occurred much later in human history in southern China. This gene has also spread, but not as far or as thoroughly because of its more recent origin. Both the American Indians and the Australian aborigines, who seem to have had an Asian origin, are practically lacking in the gene for B. They seem to have migrated before the appearance of the mutation in Asia.

In Italy and surrounding regions of the Mediterranean the gene for thalassemia causes a severe anemia when homozygous, but confers resistance to malaria when heterozygous. In this group, this mutation appeared and was selected for, while in central Africa it was the mutant for sickle-cell anemia that became established. There is more than one way in which a race can adapt to its environment. Among different races living under similar environmental conditions mutations may provide different genes for selection.

Migration. The migration of new members into a population plays an important part in the establishment of the gene pool. Today especially, with our efficient methods of transportation, the various populations are being altered by migration. The migrants tend to remain in isolated groups at first, but in time the barriers break down and their genes become a part of the overall gene pool of the region. The Swedes who migrated to Minnesota at first kept their own language, customs, and religion and tended to marry within their group. Associations in public schools and in other activities, however, invariably brought about intermarriage with those from other backgrounds. The Germans, Irish, Italians, Japanese, and other individual groups in the United States are gradually blending with the general population. The Jews have managed to keep a population identity by religious restrictions against marriage outside their group, but whenever young people of different sexes are associated there is bound to be some mixing. In Israel, where Jewish people from different regions have come together, it is evident that the German Jews differ from the Russian Jews, and both differ from the Spanish Jews. Despite the religious restrictions, there has been some gene flow from other people into the Jewish population.

The more different a migrant group is from the population it enters, the slower the mingling will be. In the United States the Japanese immigrants tend to blend more slowly with the others

around them than do the Germans because they are more different in appearance. The blacks, who were involuntary migrants to this country some 300 years ago, appear so different from the white population that the blending of genes has been slower than that of other racial groups. Still there has been some blending; the blacks in the United States today are distinctly different from those in Africa. One study by Bentley Glass, using blood types as an indicator, shows that the blacks in America have about 30.565% genes from the whites as a result of this gene flow. This alteration has occurred in about ten generations of contact and will accelerate, no doubt, as the lines of distinction between the two races become less defined. At the past rate of blending, in another 1600 years we will be a homogeneous population with no distinction between blacks and whites. Actually, since blending tends to accelerate as the lines of distinction become less clear, it should be a much shorter time.

Differential Reproduction. Subgroups within a population sometimes reproduce at a different rate than the rest of the population. When they reproduce faster the genes they carry will form a disproportionately large share of the gene pool of the entire population of the future. The Fiji islands were taken over by the British in the early part of this century. The British thought that the fertile valleys of the main island would be a good place to grow sugar cane, but found that labor was a problem. The Fijians, accustomed to getting their food from the sea and native plants, did not take well to the idea of working in the cane fields to earn money to buy what had been free. The British imported some Asiatic Indians to work the fields. These Indians, however, reproduced faster than the Fijians and now about half the population is Indian. Racial problems have developed. There is some blending of the two groups and in time they may become homogeneous, but the faster reproduction of the Indians will have a considerable effect on the final gene pool.

In many of the Caribbean islands the native Indians have practically disappeared because of the faster rates of reproduction of the Africans who were brought there to work the fields.

Invasion. Conquering armies can influence the gene pool of the lands they invade. Armies have typically considered the women of the region theirs for the taking as one of the spoils of war. As a result, many babies have been born with genes from the unwel-

come visitors. In recent history, the soldiers from West Pakistan left many of the women of Bangladesh pregnant and thus introduced genes from another population into the gene pool. Wars can also alter the gene pool of the invaders. Some soldiers took home wives after the invasion. Each of our recent wars has resulted in quite a number of war brides from Germany, Korea, Vietnam, and so on, thereby introducing new genes into our gene pool.

It is possible to trace the routes of invaders of Europe by the genes they left behind. The Mongols invading Europe from about A.D. 500 to A.D. 1500 left some of their genes along their way. This is evident by the rather high incidence of the B blood antigen in these regions today. The Mongols were relatively high in B, but the original Europeans were low in this antigen. In certain regions isolated by high mountains, the incidence of the B antigen is still low, probably because the invaders did not wish to cross the mountains to get at these small groups. The Basques on the western coast of Spain represent such a group.

England has a high frequency of antigen A in the south with a decreasing frequency as you go north and into Scotland. The original inhabitants retreated northward when the invaders and immigrants with high A came from the continent. Ireland shows a similar cline of high A in the east and low A in the west because of the invasions from southern England.

PROBLEMS

1. Domestic animals show greater differences between the various breeds or varieties than wild animals. What could account for this?

2. About 9% of a herd of Holstein cattle have red spots, a recessive trait, while the rest have the dominant black spots. What is the frequency of the gene for red in the population? What percentage of the cattle have black spots, but carry the gene for red spots?

3. Suppose the breeder of the above cattle wants to eliminate the red spots and prevents breeding of those with red spots for six generations. What would then be the percentage of red-spotted cattle born?

4. Suppose a dictator of a mythical country decides that blue

eyes should be eliminated as an undesirable trait. About 25% of the population have blue eyes and they are all sterilized. How many blue-eyed babies would be born the next generation? If the sterilization program were continued for ten generations how many blue-eyed babies would be born?

5. About 70% of the people of the United States detect a bitter taste when a small amount of PTC is placed in the mouth. A dominant gene is responsible for the ability to taste this chemical. What percentage of the total population are homozygous tasters and what percentage are heterozygous tasters?

6. In a wild population of minks, about 4% are albinos. These are not as fertile as the pigmented minks and have, on the average, only half as many offspring. After eight generations, what percentage of albino minks would you expect to be born?

7. The frequency of the recessive gene for Gaucher's disease in the United States population is about one in 400. Since each person has two genes for each chromosome locus, one person in each 200 carries the gene in the heterozygous state. Gaucher's is an enzyme deficiency disease which causes improper fat metabolism and great swelling of the liver and spleen. Death always comes before sexual maturity. If we assume that there is no input of this gene by mutation, nor any selective advantage of the heterozygote, how many persons will be carriers of the gene after six generations?

8. The British who settled Australia brought with them 30 pairs of rabbits, and the rabbit population there is now hundreds of thousands. Another group of settlers who came to New Zealand imported 5 pairs of rabbits, and these, too, have multiplied by the thousands. In which country do you think genetic drift might have played the greater part in creating the gene pool of the rabbits and why?

9. The people of ancient Greece, as portrayed in their works of art, were quite different from those living in Greece today. List the factors that might have brought about a change in the gene pool of those living in this region over the past 2000 years.

18. HEREDITY AND ENVIRONMENT

In the early part of this century, when the principles of heredity first began to be understood, it was assumed that genes were always expressed to the same degree and that environment was a separate influence. There were arguments as to whether some particular characteristic was due to heredity or environment. As we have gained a better understanding of heredity, however, we have come to realize that both hereditary and environmental forces are operating in the production of most traits. Few traits are due solely to heredity or environment. Genes give the potential, but they will be expressed according to the factors in the environment which act on them. In this chapter we shall see how these two great forces interact.

VARIABLE EXPRESSIVITY

Frequently a group of organisms with the same genotype with respect to a particular gene will show considerable variation in the degree of expression of the characteristic involved. Such variable expressivity is often a result of environmental influences. Let us consider some of the forces that can bring about such variability.

Vestigial Wings in *Drosophila*. A recessive autosomal gene, *vg*, causes the wings to be mere stumps provided the flies are grown at a temperature no higher than 72 degrees. An 8-degree elevation of the temperature will cause many of the flies to have wings considerably larger than the vestigial size and another 8-degree elevation will cause them to be so large that they extend beyond the abdomen (see figure 18–1). Hence it is evident that the temperature, in some way, has an influence on the degree of expressivity of this gene. In one environment it has one phenotype; in another environment the phenotype is so different that it might

Fig. 18-1. Variation in expressivity of the gene for vestigial wings in Drosophila. All these flies are homozygous for the gene, but the size of the wings varies because the flies were raised at different temperatures. The fly at left was raised at 72°F, the one in the center at 80°F, and the one at right at 88°F.

easily have been mistaken for a trait due to a different gene had it not been investigated genetically.

The Himalayan Coat Pattern in Rabbits. In rabbits, there is a recessive gene, h, which produces the Himalayan coat pattern. Usually such rabbits are white over most of the body, but the feet, ears, tail, and tip of the nose are black. The gene may show variation in expressivity, however, if the skin is subjected to unusual chilling. For instance, if a naked, newborn rabbit is exposed to a temperature of 52°F for a short time and then returned to its mother, the skin will grow out black all over the body. Similarly, if the fur is plucked from the back of a Himalayan rabbit and an ice pack is placed on this region for a time, the hair that grows back will be black. In a reverse experiment, if a foot is bandaged in such a way as to keep it warmer than normal, it will develop white hair. These results indicate that two factors are involved in the production of the coat pattern, one genetic and the other environmental.

The unusual effects described above might be explained by theorizing that the gene for this coat pattern produces an enzyme which is necessary for the formation of black pigment, but that at temperatures above 92°F it will not produce the enzyme or the enzyme will not function. The body heat keeps the skin above this critical level over most of the animal; the extremities, however, are readily chilled and thus develop black hair. The same results can also be explained by assuming that the genes for the Himalayan pattern produce an inhibitor which prevents black pigment
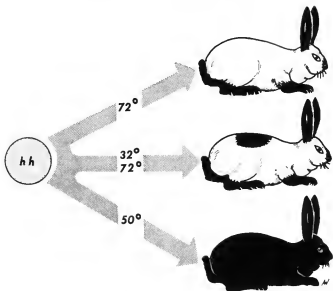
Fig. 18–2. Variable expressivity of the gene h in rabbits. The rabbit at the top has the typical Himalayan coat pattern, but the amount of black fur can be varied by altering the temperature of the skin of newborn rabbits. (From Winchester, Heredity and Your Life, Dover.)

from forming in rabbits that would otherwise be black all over. At temperatures below 92°F this theoretical inhibitor cannot function and thus black pigment is formed.

The Eyeless Gene in *Drosophila*. The above examples presented by *Drosophila* and Himalayan rabbits demonstrate how the external environment can alter the expressivity of genes. There are other cases where the environments appear to be identical, and yet there occurs variation in expressivity. Such variation must come from internal factors, usually other genes. Modifying genes, as they are called, may alter the expressivity of a gene responsible for a particular phenotypic expression, thereby changing that phenotype.

There is a recessive gene on the fourth chromosome of *Drosophila* which produces what is called the eyeless phenotype. In a group of flies homozygous for this gene, however, quite a variety of eye sizes are represented. In some flies, the eyes will be nearly as large as normal, whereas in others, the eyes may be almost or completely lacking. The majority of flies will have eyes ranging

between these two extremes. Because the variations in eye size are found among flies raised in the same vial, it appears that there are other genes at work that modify the effect of the gene for eyelessness. Through selection for both extremes of eye sizes in an eyeless stock, we can accumulate a group of modifying genes that will produce relatively large eyes in one stock and very small eyes in another.

Variable Expressivity of Human Genes. There are many human genes that have variable expressivity, for example, the dominant gene for *blue sclera* of the eyes. The sclera is a part of the eye that is normally white. Some individuals carrying this gene have a very pale blue sclera while in others it is of various shades of blue—even a blue so dark that the "whites" of the eyes look
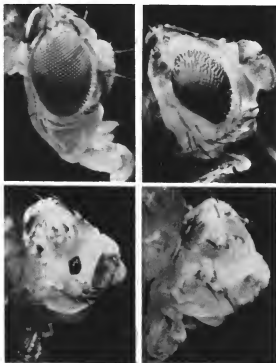
Fig. 18–3. The expressivity of the gene for eyeless in Drosophila *varies among flies raised under the same conditions, indicating an apparent influence of modifying genes.*

black. Modifying genes would seem to account for this great variability. Unfortunately, the blue sclera gene does more than affect the color of the sclera—it also may affect the bones. About three-fourths of those with blue sclera also have bones that break easily. The degree of fragility is quite variable. In some cases a bone will break if caught on the sheet while a person is turning over in bed. In others, breaks require greater strain, but in all cases the bones break more readily than in unafflicted persons. In some the condition is outgrown when adulthood is reached; in others it may persist into old age. Thus, there is a considerable variation in the degree of expressivity of this gene.

In the condition known as brachydactyly there is a shortening of the second bone of the fingers. It is brought about by a dominant gene that is lethal when homozygous. In the heterozygous condition there is considerable variation in the degree of shortening of the bone. In some the bone is so short it appears to be absent and thus the fingers seem to have only two bones—like thumbs. This disorder varies from slight shortening to the severe shortening already discussed.

Fig. 18–4. Variation in expressivity of a dominant gene causing shortening of the arms and deformity of the hands. The man on the left expresses this trait to some degree, but his son has arms shortened to mere flipperlike stumps. (Courtesy Karl A. Stiles.)

REDUCED PENETRANCE

In some cases the expressivity of a gene is so low that individuals do not show any phenotypic evidence of its presence. The human gene for blue sclera again can be used as an illustration. In about one-tenth of the people who carry this gene there is no detectable expression of it; yet about one-half of their children will exhibit some sign of blue sclera. The gene is thus said to have 90% penetrance—it shows itself in 90% of those who carry the dominant allele.

Nicked Wings in Drosophila. The recessive gene for nicked wings in Drosophila is a good example of a gene with low penetrance. The phenotypical expression of this gene is a small nick in the outer edge of the wings. The penetrance is about 3%; that is, about three out of every one hundred homozygous flies express the nicked wings. If we cross two flies with nicked wings we find the trait showing in about 3% of their offspring, yet if we cross flies from the same culture that do not have nicked wings we find the same percentage of nicked wings expressed in their offspring. Hence, we know that the genotype of the two sets of parents was the same with respect to this one gene, although one set carried the gene without expressing it.

Tremor in Chickens. A recessive gene in chicks may cause them to shake almost continuously. Hutt and Child studied 112 homozygous chickens and found that only 39 showed a detectable tremor. The others appeared perfectly normal, yet the descendants of the seemingly normal chickens also showed tremor in about the same ratio. In addition, the chickens that show the tremor reveal a variation in expressivity. Some shake so violently that they have great difficulty in taking food, while others have a tremor so slight that it is barely perceptible. Hence, the gene is one with a penetrance of about 35% and a great variation in expressivity.

Human Genes with Reduced Penetrance. The fact that many human genes have a reduced penetrance complicates the study of inheritance in relation to various diseases and abnormalities. The gene for *multiple exostoses* causes abnormal growths on the bones, but this gene has an approximate penetrance of only 60%. Thus, even though it is a dominant gene, the condition can be inherited and expressed by a child when neither parent reveals the condition.

In some cases a gene will have reduced penetrance with regard to the entire organism, but on the cellular and tissue level, its penetrance will be 100%. One form of gout is caused by a dominant gene that interferes with the regulation of uric acid level in the blood. If the uric acid level is sufficiently high, crystals of sodium urate tend to collect in the joints. There is considerable variation in expressivity, however. Some individuals with the gene suffer great pain in the joints, others experience only mild pain at infrequent times, and still others have no pain at all. All who carry the gene, however, show an abnormally high concentration of uric acid in the blood. Hence on the blood tissue level the gene has 100% penetrance, but on the organism level the penetrance is reduced.

The gene for blue sclera affects calcium metabolism and has 100% penetrance on the cellular level. However, in causing brittle bones its penetrance is 75% and, in affecting the color of the iris, about 95%.

PHENOCOPIES

Studies of heredity and environment are complicated by the fact that there may be environmentally induced characteristics that are exact copies of characteristics normally produced by genes. The term *phenocopy* has been applied to such cases.

Phenocopies in *Drosophila*. Richard Goldschmidt, of the University of California, found that many mutant phenotypes of *Drosophila* could be induced environmentally by heat shocks. For example, if larvae between 4½ to 5½ days old were exposed to a warm temperature of 35°C from 12 to 24 hours, about 70% of the adults that developed from these larvae would have scalloped wings. This characteristic also appears when the flies are homozygous for a certain gene regardless of temperature. The heat-induced and the gene-induced phenotypes are indistinguishable. When the larvae were kept until they were 7 days old and then subjected to the same heat shock, about 40% of the adults emerged with miniature wings. Miniature wings are also produced by a recessive X-linked gene.

On the basis of these results, and from other phenocopies he obtained, Goldschmidt postulated that mutant genes produce their effect by altering metabolism at specific stages of embryology. The body structures that are at a critical stage of development at this

point will be altered and therefore the adult reveals a specific phenotypic change. In his experiments, the effect of mutant genes was duplicated by an environmental alteration of the metabolism at the same critical time during embryonic development.

Harelip in Mice. In certain strains of mice, harelip appears in about one-fourth of the offspring no matter how ideal the environment of the mother may be. In other strains the abnormality under normal environmental conditions is practically unknown. This fact establishes beyond doubt that there is some hereditary background for the harelip abnormality. It is possible, however, to obtain a high incidence of harelip from the second strain by treating the pregnant females in certain ways at a time when the embryos within their bodies are at a specific stage of development. The treatments can be quite varied, for it is the time of application that is the important factor. Injections of cortisone, feeding a diet deficient in certain vitamins, subjecting the females to an atmosphere of low oxygen concentration, and removal of some of the amniotic fluid around the embryos are examples of the treatments that have been used. All interfere with normal metabolism at a time when the upper lips of the embryos are at the stage of fusion. The lips will not fuse properly and the time for fusion passes. Thereafter, even if normal metabolism is restored, the fusion does not take place, and harelip results. In the strains where harelip occurs without the environmentally induced alterations of metabolism, we can assume that the genes accomplish the same thing.

Human Phenocopies. Quite a number of inherited human traits may also be induced by environment as phenocopies. **Rickets** is generally thought of as caused by an insufficient amount of vitamin D in the body. This vitamin is necessary for the normal absorption of calcium by the bones and when it is deficient the bones will be soft and deformed in shape. Some children, however, may receive sufficient quantities of vitamin D, yet still have rickets because they cannot properly utilize the vitamin they receive or produce in the skin. They can be saved from the disease by massive doses of vitamin D. Although vitamin D resistant rickets is less common, the environmentally induced form of the disease may be considered a phenocopy.

Hydrocephalus (water on the brain) is an affliction caused by excessive pressure of the fluid within the brain during fetal development. Because the bones of the cranium are soft at this time, they can expand, and the baby is born with a very large top of the head.

In the normal fetus the pressure is kept at the proper level by absorption of the fluid by the membranes lining the ventricles, or brain cavities. An autosomal recessive gene causes a thickening of these membranes, thus impairing their ability to absorb the fluid. In some cases, however, no genes are involved. If a pregnant woman has certain virus infections or receives heavy radiation at a critical time during the development of the membranes they may become thickened and the cranium will swell.

TWIN STUDIES

Studies of human twins and other multiple births provide geneticists an opportunity to determine the effects of heredity and environment. Identical twins, having descended from one fertilized egg, have identical genes; therefore, any differences they manifest are obviously due to environmental agents. Fraternal twins, on the other hand, originate as two separate fertilized eggs and will differ in many of their genes. Thus, differences fraternal twins manifest can be due to heredity, environment, or a combination of both. Fortunately, from the standpoint of genetic studies there are a few cases in which identical twins have been separated shortly after birth and raised in different environments. If we assume that twins of the same sex receive about the same environment when raised in the same household, we have three sets of circumstances for examination. First, we have children with the same heredity and approximately the same environment—the identical twins raised together. Second, we have children with some differences in heredity and approximately the same environment—the fraternal twins of the same sex raised together. Finally, we have children with the same heredity and different environments—identical twins raised apart. Comparisons of these three groups have provided insight into the influence of heredity and environment on different characteristics.

Results Obtained from Twin Studies. The first extensive investigation of characteristics of different types of twins was done by H. H. Newman at the University of Chicago. Since that time literally thousands of twins have been studied with respect to those characteristics that might have some basis in heredity. The results of some of these investigations in terms of differences are given in

table 18–1. For comparison a fourth group is included. These are the "sibs," brothers or sisters who are not twins. This group is of different ages, but their gene similarity is the same as for fraternal twins; when allowance is made for the age differences we would expect them to show about the same variability as fraternal twins. Because sex makes such a difference in an individual's characteristics and environment, the sibs and fraternal twins considered in this study are of the same sex. Identical twins, of course, are always of the same sex.

The results indicate that heredity plays a major role in determining physical characteristics, for example, body height. Fraternal twins of the same sex show a much greater difference then do identical twins even though the environmental agents seem to be the same for the members of each set. Even when identical twins are reared apart they show a similarity in stature which is almost the same as among those reared together. Environment seems to play a greater role in determining the IQ scores—the identical twins reared apart reveal a considerable variation from those reared together. Still, the fact that fraternals are more variable than identicals reared together shows that heredity does play an important role.

Concordance. Many studies of twins are made on the basis of concordance, or the percentage of similarity. Police records were

TABLE 18–1
DIFFERENCES BETWEEN TWINS AND SIBS

	Identical	Fraternal	Sibs	Identical Reared Apart
Body height				
(difference in cm)	1.7	4.4	4.5	1.8
Body weight				
(difference in lb)	4.1	10.0	10.4	9.9
Total finger ridges	5.9	22.3	—	—
Age of first menstruation				
(difference in months)	2.8	12.0	12.9	—
IQ (Binet)				
(difference in points)	5.9	9.9	9.8	8.2

examined to find individuals convicted of major crimes who possessed a twin brother or sister. A study was then made to determine whether the twin also had a criminal record and whether the twins involved were identical or fraternal. In 68% of the cases in which the twins were identical, both were found to have a criminal record. In the cases in which the twin was fraternal and of the same sex, only 28% were found to have a criminal record. A similar study in Germany gave concordance of 68 and 38, respectively.

Environment and Heredity in Disease. One of the most valuable pieces of information stemming from the twin studies has been the effect of heredity on various human disease and afflictions. The results of some of these studies are summarized in table 18–2 with the similarity expressed in terms of concordance.

These studies reveal that in some cases, even the germ diseases, which one might think would be conditioned primarily by environment, are related to heredity. Certainly the organic diseases, such as cancer and diabetes, have an important relationship to heredity, but here again some environmental influence can be noted. The concordance for rickets in the table indicates the role played by heredity in the disease.

The more we study heredity and environment the more we realize that each plays a vital role in the development of the individual—few characteristics can be assigned solely to one or the other.

TABLE 18–2
TWIN CONCORDANCE WITH RESPECT TO DISEASE
AND BODY ABNORMALITIES

Characteristic	Identical	Fraternal
Harelip	33	5
Mongolism	89	6
Mental retardation	97	37
Schizophrenia	86	15
Cancer	61	44
Site of cancer (when both have cancer)	95	58
Measles	95	87
Tuberculosis	87	25
Diabetes mellitus	84	37
Rickets	88	22

Fig. 18–5. Both of these rats have been fed the same diet, yet the one on the left is healthy, while the one on the right has rickets. They differ genetically in the amount of vitamin D required to prevent rickets.

PROBLEMS

1. Describe a human trait that observation shows is definitely influenced by heredity, yet which shows variable expressivity. What environmental factors do you think might be involved in the variations in expressivity?

2. Polydactyly is a human trait characterized by extra fingers or toes. Family pedigree studies indicate dominant inheritance. A man has six fingers on each hand, but has a daughter who is normal. Two of his daughter's four children, however, have the extra fingers. How can you explain this in the light of the facts considered in this chapter?

3. In domestic swine, a recessive gene causes cleft palate, but it has only a 20% penetrance. A farmer's breeding stock are all heterozygous for this gene. What percentage of the pigs will be born with cleft palate?

4. A recessive gene in the domestic fowl causes rumplessness, the absence of a rear end. Phenocopies of this trait can be induced by injecting insulin into incubating eggs. Suppose you inject insulin into eggs from a breed that carries the gene. How can you determine which of the rumpless chickens that hatch are phenocopies induced by the insulin and which are due to heredity?

5. Studies on human identical twins show that when one has harelip, the other will also have it in 33% of the cases. Fraternal twins of the same sex, however, have such a concordance of only 5%. Evaluate the possible roles of heredity and environment from these results.

6. In twin studies for determining the effects of heredity and environment, those of opposite sex are not included. Why are these not used?

ANSWERS TO PROBLEMS

CHAPTER 1

1. Cattle are far from ideal for genetic breeding experiments. They have a relatively long life cycle, they usually have only one offspring at each birth, and they require considerable room, feed, and care to raise.

2. Pedigrees can be used to record the results of crosses already made, thus obviating the long process of experimental breeding.

3. The use of antibiotics, immunization techniques, and sanitary practices have greatly reduced the number of infectious diseases requiring the attention of physicians. At the same time, the many discoveries of the nature of inherited diseases have led to methods of treating them. In the past, inherited diseases were frequently passed over because it was felt that nothing could be done to prevent them.

4. The conditions for cultivation in Asia are different from those in the United States and a variety that may do very well here might, when grown in Asia, have problems of disease, lack of critical elements in the soil, differences in rainfall and temperature, and availability of proper fertilizers.

CHAPTER 2

1. With the discovery of the method of sperm and egg formation, no way can be found for the transfer of acquired characteristics to the reproductive cells. The experiments on the removal of tails from mice and on the transportation of fertilized eggs into a proxy mother give further evidence.

2. Lysenko's proposal was really a rehash of Lamarck's concept of "use and disuse," which involved inheritance of acquired char-

acteristics. It also included some of Aristotle's old ideas of transmission of traits from individual body parts to the reproductive cells.

3. Lamarck would have contended that as a giraffe stretched its neck in reaching for food its neck became longer. This extra length was passed to the offspring and after many generations of this the necks became very long. Darwin would have said that giraffes with shorter necks would have starved because they could not reach the leaves of tall trees, whereas giraffes with long necks survived and passed the trait for long neck to their offspring. As to how the trait got into the germ plasm, he would have speculated that a tiny "pangene" produced in the neck migrated to the reproductive organs. De Vries would have maintained that random mutation of genes caused some giraffes to have longer necks; these had the advantage over the others and survived to transmit the mutant genes to their offspring.

CHAPTER 3

1. When the core of nucleic acid from one virus is placed in the protein coat of another, the virus formed by this union has the characteristics of the virus which furnished the core. Also, the fact that only the nucleic acid is emptied into a cell which is infected by a virus shows that this part carries all the information needed to form new virus particles.

2. In transformation, the bacteria take in new DNA from dead bacteria by engulfing it, while in transduction the DNA is brought in by virus particles from their previous bacterial host.

3. The protein coat contains the part which must become attached to the cell to be infected. Without this coat the nucleic acid portion has no way to enter other cells.

4. Species differ greatly in their total number of genes according to their complexity so the quantity of DNA would be in proportion to the number of genes.

5. The complementary bases would be thymine, adenine, guanine, and thymine.

6. Adenine and thymine are always paired in the DNA molecule, so when one is present the other will be present also. Cytosine, however, is a member of another base pair and can be present in quantities different from those of adenine.

CHAPTER 4

1. The telophase chromosomes become longer and thinner by uncoiling which is the reverse of the shortening and thickening in the prophase. The telophase is different in that the chromosomes are single and not double.

2. Prophase 8, anaphase 16, prophase of first meiosis 8, telophase of second meiosis 8, prophase of second meiosis 4.

3. Without spindle fibers the centromeres of the chromosomes could not line up in a row on a spindle. Such a cell would have duplicated chromosomes which could not separate in an orderly fashion in mitosis.

4. G_2 of interphase 160,000, G_1 of secondary oocyte 80,000, anaphase of first meiosis 160,000, telophase of second meiosis 80,000, spermatid 40,000.

5. No, the offspring would differ from the mother genetically. Half of the mother's genes are lost to the first polar body, so the second polar body receives genes that are duplicates of the genes in the egg.

6. There could be no pairing of like chromosomes in meiosis and there would be an irregular assortment of chromosomes in the gametes. It would not be possible for any zygote to get a full complement of genes; it would get two of some kinds of genes and none of others.

7. There cannot be an even matching of chromosomes so the chance that any gamete would obtain a full set of genes is infinitesimal.

8. All genes are expressed in haploid organisms, but when diploid there is a good chance that any harmful gene will be compensated for by the action of a mate which has a normal effect.

CHAPTER 5

1. Cross pure-breeding rose-combed chickens to pure-breeding single-combed chickens. Whichever type of comb appears in the offspring is apparently dominant. This tentative conclusion can be confirmed by an *inter se* cross of these F_1s. This should give the 3:1 ratio in the F_2, the smaller number being the recessive trait.

2. Allow $S =$ rose and $s =$ single comb.

$$SS \times ss = \text{all } Ss \text{ (rose-combed) in } F_1.$$

$$Ss \times Ss = 1 \ SS{:}2 \ Ss{:}1 \ ss \quad \text{(Genotype in } F_2\text{)}$$

Phenotype—3 rose:1 single

3. A = free earlobes; a = attached earlobes.

Woman $aa \times$ Man $Aa = 1 \ Aa{:} 1 \ aa$ Genotype

Phenotype—1 free:1 attached

4. The solid color would be easier to establish because all the farmer needs to do is breed only solid-colored hogs; all of these must be homozygous or they would not be solid-colored. The belted body is harder because some of the belted hogs may carry the recessive allele for solid and testcrosses would have to be made to identify those heterozygous carriers and eliminate them from the breeding stock.

5. This is obviously a case of intermediate inheritance because the F_2 are in an approximate ratio of 1:2:1. The diagram can be the checkerboard or any other method given in this chapter.

6. P—ptosis; p—normal eyelids (Man is almost certainly heterozygous because the gene for ptosis is so rare.)

Genotype—$Pp \times pp = 1 \ Pp{:}1 \ pp$
Phenotype—1 ptosis:1 normal eyelids

7. With such tests, counselors can better advise clients as to their chance of bearing defective children. When both parents are carriers, one-fourth of their offspring will express the recessive trait. If either is not a carrier then there is no chance of the defect in their children.

8. Anirida: structural because the iris is a structure formed by genes.

   Albinism: functional because an enzyme to produce melanin is not working.

   Elliptical red blood cells: structural because the defect is in the formation of cells and not the result of an enzyme deficiency.

9. Recessive because there is evidently a lack of an enzyme to break down cystine in the cells and a single gene could make all the enzyme needed.

10. By crossing the cattle he has he will get half roans and half whites. Crossing the roans should give him some reds in the next generation. Then he should pick two reds and continue to breed from these.

CHAPTER 6

1. Using the forked-line method, the results would be:

¾ erect-eared ——— ¾ barkers   = ⁹⁄₁₆ erect-eared barkers
             ——— ¼ silent   = ³⁄₁₆ erect-eared silent

¼ droop-eared ——— ¾ barkers   = ³⁄₁₆ droop-eared barkers
              ——— ¼ silent   = ¹⁄₁₆ droop-eared silent

2. Because either pp or ii makes platinum the results are:

¾ brown ($P-$) ——— ¾ brown ($I-$)   = ⁹⁄₁₆ brown ($P-I-$)
              ——— ¼ platinum (ii) = ³⁄₁₆ platinum ($P-ii$)

¼ platinum (pp) ——— ¾ brown ($I-$)   = ³⁄₁₆ platinum ($ppIi$)
                 ——— ¼ platinum (ii) = ¹⁄₁₆ platinum ($ppii$)

Phenotypic ratio—9 brown:7 platinum

3. The results are:

½ blaze ——— ½ nonalbino = ¼ blaze
        ——— ½ albino   = ¼ albino (albino cannot show)

½ nonblaze ——— ½ nonalbino = ¼ normal (nonblaze and nonalbino)
           ——— ½ albino   = ¼ albino

Phenotypic ratio—1 blaze:1 normal:2 albino

4. The results are:

¾ pea ——— ¾ rose   = ⁹⁄₁₆ walnut
      ——— ¼ single = ³⁄₁₆ pea

¼ single ——— ¾ rose   = ³⁄₁₆ rose
         ——— ¼ single = ¹⁄₁₆ single

5. The results are:

½ black ——— ½ trotter $=$ ¼ black trotter
         ——— ½ pacer $=$ ¼ black pacer

½ chestnut ——— ½ trotter $=$ ¼ chestnut trotter
           ——— ½ pacer $=$ ¼ chestnut pacer

6. The genotype of the woman would be $AaBb$ while that of the man would most likely be $aaBB$ (or $AABb$). The offspring from these genotypes would be

¼ $AaBB$: ¼ $AabB$: ¼ $aaBB$: ¼ $aabB$
Phenotypic ratio— ¾ normal : ¾ deaf

7. Genes involved: P—pigmented eyes, p—unpigmented (can use traditional B and b) M_l^H heavy melanin deposits, M_l^L light melanin deposits, M_t^H heavy, M_t^L light.

Green-eyed parent: $PpM_l^L M_l^L M_t^L M_t^L$
Black-eyed parent: $PpM_l^H M_l^H M_t^H M_t^H$
Blue-eyed child: $ppM_l^L M_l^H M_t^L M_t^H$
Brown-eyed child: $P\text{—}M_l^L M_l^H M_t^H M_t^H$

CHAPTER 7

1. Each generation receives half of the genes from each parent, and there are three generations. The answer would therefore be $(½)^3$ or ⅛. *Note:* The gene for potato nose is so rare that the chance that the man is homozygous is too small to be considered a probability.

2. $\frac{1}{30} \times ¼ = \frac{1}{120}$

3. Multiply $\frac{3}{7}$ by itself to get the chance that both carry the recessive gene and then by ¼, the chance that the recessive trait will appear in a child of heterozygous parents. Thus,

$$\frac{3}{7} \times \frac{3}{7} \times ¼ = \frac{9}{196}$$

4. The chance that the child received the gene from his father is ½ and the chance that he will express the trait if he received the gene is $\frac{1}{10}$. Thus,

$$½ \times \frac{1}{10} = \frac{1}{20}$$

Note: The dominant gene is so rare that the chance the man will have two of them is such a small fraction that it can be ignored.

5. Take the square root of 10,000 and get $\frac{1}{100}$. Then, since each person carries two genes at this chromosome locus add $\frac{1}{100} + \frac{1}{100}$ and get $\frac{1}{50}$ as the chance of any one person being a carrier.

6. $\frac{1}{20} \times \frac{1}{20} \times \frac{1}{4} = \frac{1}{1600}$ which is the chance that the first baby born will have cystic fibrosis. Square this figure to get the chance that the first two will both have the disease. This gives a probability of only $\frac{1}{2,560,000}$. To get the chance that either one of the two will have it, add the chances: $\frac{1}{1600} + \frac{1}{1600} = \frac{1}{800}$.

7. The chance for deafness from one of the genes is $\frac{1}{4}$ so the chance of deafness from either one of the two would be the sum of the individual probabilities: $\frac{1}{4} + \frac{1}{4} = \frac{1}{2}$.

8. For the first couple the chance for the desired sequence would be $(\frac{1}{2})^3$ or $\frac{1}{8}$, since the chance is $\frac{1}{2}$ for each sex at each birth, a permutation. For the second couple, a combination is involved, set up as follows:

$$n = 3 \quad s \text{ (boys)} = 2 \quad t \text{ (girls)} = 1 \quad p = \frac{1}{2} \quad q = \frac{1}{2}$$

$$\frac{3 \times 2 \times 1}{2 \times 1 \times 1} \, (\frac{1}{2})^2 \times \frac{1}{2} = \frac{3}{8}$$

To use the binomial method $(p + q)^n$ we select the term

$$3p^2q = 3 \times \frac{1}{4} \times \frac{1}{2} = \frac{3}{8}$$

9. p = albino girl = $\frac{1}{4}$ (chance of albinism) $\times \frac{1}{2}$ (chance of girl) = $\frac{1}{8}$

q = normal boy = $\frac{3}{4} \times \frac{1}{2} = \frac{3}{8}$.

Choose from binomial $3p^2q$. Then

$$3 \times \frac{1}{64} \times \frac{3}{8} = \frac{9}{512}$$

10. Expected ratio from these obviously heterozygous parents is 1:2:1.

$$\frac{10' \text{ (total children)}}{4' \, 4' \, 2'} \, (\frac{1}{2})^4 \, (\frac{1}{2})^4 \, (\frac{1}{4})^2 = \frac{1}{910}$$

11. Chi-square is determined as follows:

Blood Type	Observed	Expected	d^2	$\dfrac{d^2}{e}$
A	50	60	100	1.66
not A	50	40	100	2.50
				$\chi^2 = \overline{4.16}$

$$5\% > P > 1\% \quad P = 4.545\%$$

Because the probability of this great a deviation occurring by chance is less than 5%, we would consider this a significant deviation and assume that there has been some gene flow from surrounding people. (It is only slightly below 5%, however, so it is not *highly* significant.)

12. The chi-square would be as follows:

Observed	Expected	d^2	$\dfrac{d^2}{e}$
24	25	1	0.04
26	25	1	0.04
21	25	16	0.64
29	25	16	0.64
			$\chi^2 = \overline{1.36}$

$$80\% > P > 70\% \quad P = 71\%$$

Since P is far above the 5% level of significance, we can be assured that the small deviations obtained were due merely to chance and this is representative of the 1:1:1:1 ratio.

13. Chi-square is 38.6, which gives P a value of less than 1. The difference between the two groups is therefore significant.

CHAPTER 8

1. A bacterium becomes transformed into a donor or male cell.

2. A *Bonellia* intersex is produced if a larva is attached to the proboscis of a female for a time and then is broken away.

3. In *Drosophila* the Y chromosome seems to have no role in sex determination, but it is necessary for male fertility. In humans it carries male-determining genes because there are no males without a Y chromosome.

4. Two sperm would be XY and two would have no sex chromosomes. When an XY sperm unites with a normal egg (with one X), the individual is XXY (Klinefelter's syndrome). When a sperm with no sex chromosomes unites with an egg, the individual is XO (Turner's syndrome).

5. In the AAAAXXXY fly, AAAA would have a male-determining value of 4, while XXX would have a female-determining value of 4.5, so it would be female, although perhaps not fully as female as normal. The AAAAXXYY fly would be 4 for maleness and 3 for femaleness, so it should be a male.

6. This would be a partial Turner's syndrome. The X chromosome balance is between the XX of the normal female and the XO of Turner's.

7. The sperm would be half W and half Z while the eggs fertilized would be the same. The results: ZW × ZW = WW (dies): 2 ZW (females): ZZ (male). Of the chicks that hatch, the ratio would be 2 females : 1 male.

8. Drones arise from unfertilized eggs, therefore they have no father, yet the queen that produced the eggs had a father, so a drone has a grandfather.

9. A. XXY, Klinefelter's syndrome. B. Trisomy-X, superfemale. C. XO, Turner's syndrome. D. XX, normal female. E. XYY, male with possible antisocial tendencies.

10. The hermaphrodite would be authentic because this condition does appear in human beings, but the "half-and-half" person would be a fake because hormones distribute sex characteristics evenly over the body.

11. The number of males will be higher when conditions for development are best. This is more likely to be in the first born than in the sixth born because repeated pregnancies, especially when coming close together, plus increasing age will cause a woman to be in poorer reproductive condition and a male fetus will not have as good a chance of survival.

CHAPTER 9

1. Use w for white and W for red. $Ww × wW = Ww$ (red-eyed female) + WY (red-eyed male) + ww (white-eyed female) + wY (white-eyed male).

2. $hh × HY = hH$ (normal daughters) + hY (hemophiliac sons).

3. $Dd \times dY = Dd$ (normal daughter) $+ DY$ (normal son) $+ dd$ (color-blind daughter) $+ dY$ (color-blind son).

4. The parents' genotypes are dP/Dp and DP/Y. The sons would be dP/Y and Dp/Y; the daughters, dP/DP and Dp/DP (all normal vision).

5. Chance of son ($\frac{1}{2}$) $\times$ chance of optic atrophy (1) $\times$ chance of normal pigmentation $\frac{3}{4} = \frac{3}{8}$. Chance of daughter ($\frac{1}{2}$) $\times$ optic atrophy (0) $\times$ normal pigmentation $\frac{3}{4} = \frac{3}{8}$. Chance of son ($\frac{1}{2}$) $\times$ optic atrophy (1) $\times$ albinism $\frac{1}{4} = \frac{1}{8}$.

6. Because this is intermediate, use symbol C^B for black and C^Y for yellow. $C^B C^Y \times C^Y Y = C^B C^Y + C^B Y + C^Y C^Y + C^Y Y = 1$ tortoise-shell female:1 black male:1 yellow female:1 yellow male.

7. The female is the heterogametic sex in birds. Hence:

$$BZ \times bb = Bb + bZ = 1 \text{ barred male:1 nonbarred female}$$

8. It would be twice the frequency in the men, or 60%. This is because each woman has two X chromosomes and therefore double the chance for carrying this gene.

9. The woman must have one gene for normal color vision, received from her father, but must also carry the gene for deutan color blindness. By chance, most of the Barr bodies of the cells in her retina must include the gene for normal color vision, so most of her cones for green vision are defective.

10. Both of these cattle would be homozygous because mahogany and white is recessive in the female and dominant in the male. Therefore, $MM \times mm = Mm$. Males would be mahogany and white and females would be red and white.

11. The gene for horns (H) is dominant in the males and recessive in the females. Because some of the male offspring have horns, the female parent must have been heterozygous, Hh, while the male parent with no horns would be hh.

12. Drones are haploid for all genes, therefore the drone would be C. The queen would have to be cc. Drone offspring would all be c, chartreuse, while female offspring would be Cc, brown.

13. The female does not carry any alleles of these genes; thus, if any of the genes were vital, the females could not survive. Because most genes are vital as shown by the fact that a loss of even a few from any one chromosome causes death, the Y would not carry many genes.

14. Assume L is the gene for long, which is dominant in woman and recessive in man. The woman would be ll, the man, LL. The

children would all be *Ll* and have a long finger if girls and a short finger if boys.

15. The mother must be homozygous for a dominant gene for a very hairy chest even though she does not express the trait.

CHAPTER 10

1. Cross cinnabar with brown and observe the offspring. If they have the wild-type red eyes, the two genes involved must lie at different loci and are not alleles. If the offspring have a shade of eye between cinnabar and brown, they are alleles. Also, they would be alleles if the eyes were either cinnabar or brown which would be the case if one of these genes was dominant to the other.

2. They could not express both, but could express one or the other. The gene for full color and that for chinchilla are both dominant to the genes for albinism and Himalayan. Hence both parents would be heterozygous for the gene for albinism and have an albino offspring. The same is true for Himalayan coat, but both parents could not carry both recessive genes.

3. Genotypes would be *ABC/ABC* × *abc/abc* = *ABC/abc*. Fruit would be 5½ ounces because it would contain three contributing genes, each adding ½ ounce to the 4 ounces of the size in the parent with the smaller fruit.

4. The 5-ounce parent would be *ABc/abc* and the 5½-ounce parent, *ABC/abc*. The 6½-ounce offspring could receive genes *ABC/ABC*.

5. Both parents would carry some genes for high IQ and some for a lower IQ. By chance, one child might receive most of the genes for high IQ from both parents and have a very high potential. The other children would receive a distribution somewhat like the parents.

6. The green-eyed person evidently carries the gene for pigmentation of the iris, but also has genes for very light melanin deposits. The blue-eyed mate would be homozygous for nonpigmented iris, but could carry genes for heavy pigment, if pigment were present; hence, the child with rather dark eyes. Two green-eyed parents, on the other hand, would both carry genes for very light pigmentation, so there is no way they could pass genes for dark pigmentation to their children.

7. There would be five pairs of genes, a total of ten genes. The

classes of offspring include one more than the total number of genes involved.

8. The darkest possible child would receive all the genes for heavy pigmentation from both parents and so would be $10 + 30 = 40$. The lightest possible would be 0. More than half of the genes in each parent are for the lightest pigmentation and all of these could go to one child.

9. You could assume that a threshold of at least five contributing genes would be necessary to make brown eyes. Those with three or less of these would have blue eyes. Most marriages between brown-eyed persons result in children with at least four of these contributing genes, but as occasional child would have three when both parents carried several of the noncontributing genes.

10. $V = 0.625$

$\sigma = 0.25$

$s_{\bar{x}} = 0.03125$

11. $V = 0.125$

$\sigma = 0.35$

$s_{\bar{x}} = 0.04375$

12. Yes, standard errors do not overlap.

13. Women have more variation; they have a higher standard deviation.

CHAPTER 11

1. No, he could have been the father because both he and his wife could have carried the gene a, and it could have become homozygous in a child.

2. Yes, they would indicate that the man was not the father. The fact that his blood did not react with anti-H showed that he was homozygous for the gene A and therefore could not have carried a.

3. The genes $A^B A^B$, $H-$, and $Se-$. He would be homozygous for A^B because he did not react with anti-H. He must have had at least one H, however, and one Se. The second allele of the latter two could not be determined from these results.

4. He is telling the truth because his blood reacted with anti-H. This means that he is heterozygous for the gene A^B while the extortionist had to be homozygous for this gene.

5. No. Although the sperm could have cde, there is no way the

egg could carry these three genes, so the child would have to be positive for D.

6. This could not have been the child of these parents. While the ABO and the Rh tests indicate a possibility, the child is MN and neither parent carried the gene for N.

7. Tell her there is nothing to worry about. The fact that she had erythroblastosis as a baby shows that she is Rh positive, and only Rh negative women need to worry about Rh-induced erythroblastosis.

8. The Rh positives should tend to increase, since there would no longer be the elimination of many of these through death by erythroblastosis.

CHAPTER 12

1. There would be 12 linkage groups. The grasshopper has the XO method of sex determination—the male has only one X chromosome, but this still represents a linkage group along with the 11 pairs of autosomes.

2. $\frac{1}{20}$. Since there are 20 linkage groups, the chance is one in twenty that the belted body gene will lie on the particular chromosome occupied by the gene for waltzing.

3. No. These results approximate a 1:1:1:1 ratio which is expected when there is free assortment of genes in the F_1 hybrid.

4. The genes are linked because the results show about a 1:1 ratio for the parental types, but the recombinations are much less in frequency. The crossover percentage is 12 (96 crossovers in 800 flies).

5. At 62. $56 + 6 = 62$ or $36 + 26 = 62$.

6. Since gl stands alone in one of the double crossover classes, we know that it is located in the center. We recognize the double crossovers because these classes are smaller (4 and 7) than the other classes. Crossovers between v and gl are 18.3% of the total. Between gl and va the crossover percentage is 13.6. We can then place the genes on a chromosome map as follows:

```
|        18.3        |           13.6           |
+--------------------+--------------------------+
v                    gl                         va
```

7. Expected percent if no interference: $0.183 \times 0.136 = 0.025$ or 2.5%

Expected number of doubles: 2.5% of 726 = 18
Obtained number of doubles: 11
Coincidence of interference: 11/18 = 0.6

8. No. It makes no difference whether the genes for C and D antigens are on the same or different chromosomes. The antigens are present in both cases.

CHAPTER 13

1. The diagram should show one of the X chromosomes with a deletion which includes the region that contained the gene S. The fly in the offspring without Star eyes would have received this deleted chromosome from the Star-eyed parent and a full chromosome 2 with the recessive allele, s, from the other parent.

2. An inversion has occurred in the center of the chromosome so that the two middle genes are in reverse order.

3. Animals have no way of propagating offspring from these islands of tetraploid tissue as can plants.

4. Two wild species might both produce diploid branches which would bear diploid gametes. Should two such gametes from different species come together, a new allotetraploid species would arise.

5. In allotetraploids there are only two of each kind of chromosome, so there will very likely be a normal alignment in meiosis. Autotetraploids have four of each kind of chromosome and there is a chance that three may go to one pole and only one to the other. Triploids, of course, get many assortments; the gametes will receive two of some chromosomes and one of others and therefore are not viable.

6. Half of the offspring would be $ey\ ey^+$ and would have normal eyes. The other half would not get the gene for normal eyes from the monosomic parent and would be ey. They would be eyeless.

7. Six would have Down's syndrome, according to probability. Half of the eggs from such females should receive two 21s and the other half should receive the usual chromosome 21. When fertilized with normal sperm, the eggs with two 21s would produce children with the syndrome while those with one 21 would yield normal children.

8. They are longer because they are uncoiled interphase chromosomes. They are thicker because they are paired and have duplicated many times over.

9. When a ring chromosome is formed there is a double deletion of the terminal ends of the chromosome. It is this loss of genes that causes the abnormality.

10. When Down's syndrome is due to nondisjunction, it is much more likely to occur in females because of the long time between the two meioses. When it is due to a translocation, however, it can be carried just as often by the father as by the mother.

CHAPTER 14

1. Only 16 possible doublet combinations of the four bases are possible, but there are 20 different amino acids. Hence, there would not be enough combinations to code all the amino acids. Doublet combinations would be $4^2 = 16$, while triplet combinations would be $4^3 = 64$, giving more than enough possible combinations.

2. UAG for the m-RNA and AUC for the t-RNA.

3. Yes. The transfer-RNA is the same in all cells since the 20 amino acids to be carried are the same in all. Messenger-RNA, however, would be different since guinea pig proteins are different from those of human cells.

4. Since there are three bases to each codon for one amino acid the answer would be $147 \times 3 = 441$.

5. When cystine becomes high in the blood some will enter the liver cells. There it unites with the repressor, thus permitting the operator gene to turn on the genes for the production of enzymes needed to break down cystine.

6. Antibiotics inhibit m-RNA formation, but they are selective. Those that cannot be used on human beings evidently inhibit m-RNA formation in human cells as well as in bacterial cells. Other antibiotics would work on bacterial cells and not on human cells.

7. It would not be able to respond by producing the enzyme to digest the lactose, nor to increase the permeability of the cell to lactose. The structural genes could not produce their m-RNA without stimulation from the operator.

8. These would have the type of albinism due to poor tyrosine absorption by the cells. With extra tyrosine there would be some absorption and some melanin would be produced because the enzymes for melanin production are in the cell.

9. The high level of phenylalanine in her blood would damage the brain of the child developing in her body if she did not return to the diet.

10. We can withhold lactose from a baby's diet by simply stopping milk. We cannot withhold tyrosine, however, since this is in most protein food and can be produced from phenylalanine. Too many vital body products must come from tyrosine to attempt to eliminate it from the diet.

11. You could fertilize flowers on this branch with pollen from a normal branch. If all the seed grew into plants with leaves of the yellow color, you could assume this was cytoplasmic inheritance. Such tests should be carried for several generations to be sure a dominant nuclear gene was not involved.

CHAPTER 15

1. He could breed the tom turkey to hens in the flock and then inbreed the offspring. If the trait was due to a dominant mutant, half of the first generation would show the trait. If it was recessive, then it would appear in about one-fourth of the second generation. If it did not appear in either generation, it might be an environmentally induced characteristic.

2. Special tests of the proteins will show the amino acid composition of the polypeptide chains.

3. Several triplet bases may code the same amino acid, so an alteration of the bases might code the same amino acid as before.

4. Reverse mutations must be a change in a specific base, while direct mutations can be changes anywhere along the length of the gene.

5. A mutation (change in the bases of the DNA) will result in a change in the amino acid sequence of the polypeptide chain codes by the gene. The result is more likely to be so extreme as to cause death than to be so mild that a visible change in phenotype results.

6. No. Bacteria have only one gene replication per generation cycle, while in humans there are hundreds of such replications in each generation cycle.

7. The mutation might so alter the virus protein that it is not affected by the antibodies produced against the former strain.

8. The chemicals could cause mutations that can lead to cancer.

CHAPTER 16

1. Plant and animal breeders can select those mutations they want to propagate and discard the many harmful ones, but all human life is preserved and allowed to reproduce if it is able.

2. Ultraviolet light has very low penetrance compared to high-energy radiation so, while it can penetrate bacterial cells and cause mutations, it cannot penetrate deeply enough to have much mutagenic effect on humans.

3. Cancer, embryo abnormalities, and mutations or chromosome aberrations are all expressions of genetic changes within cells. Hence, an agent that would cause one abnormality is likely to cause the others.

4. Oxygen is required for the formation of certain reactive chemicals which can cause mutations, so if the mutagenic action of radiation is chemical, it would be expected to decrease with decreased oxygen, and it does.

5. The mutation of a gene is a single change, but permanent chromosome aberrations often involve rearrangements resulting from at least two breaks within the same cell. The chance of two breaks in the same cell is greater when the radiation is more intense.

6. Embryonic cells are growing and dividing much faster than the cells of adults and, because actively dividing cells are particularly sensitive to radiation damage, the embryo is more readily damaged.

7. The proportion of girls would drop because only the female embryos would receive the X carrying the dominant mutation from the father. The males receive their single X from the mother only.

8. Even a little extra radiation would increase the mutation rate slightly and, considering the entire world's population, quite a few mutations would be induced.

CHAPTER 17

1. There is more random breeding among wild animals, usually only geographical separation allowing assortive mating. In domestic animals, however, like forms are commonly bred together in an

imposed assortive mating, so the breeds can be established and remain very different.

2. If 9% have red spots, the frequency of the gene for red would be the square root of this figure, or 30%. The frequency of the dominant gene for black would be 70%, so the frequency of heterozygotes with black spots would be 42%. ($2pq = 2 \times 0.70 \times 0.30 = 0.42$.)

3.
$$q_6 = \frac{q_0}{1 + 6q_0} = \frac{0.30}{1 + 6 \times 0.30} = 0.107$$

10.7% is the gene frequency for red after six generations of selection, so the number of red-spotted cattle is the square of this, or 1.14%.

4. Since 24% have blue eyes, the frequency of the gene for blue is 50%, the square root of 25%. The number of babies born with blue eyes after the first generation of selection would be:

$$q_1 = \frac{0.50}{1 + 1 \times 0.50} = 0.333 \text{ frequency of gene for blue}$$

$(0.333)^2 = 0.111$, or 11.1% babies with blue eyes.

After ten generations of selection it would be:

$$q_{10} = \frac{0.50}{1 + 10 \times 0.50} = 0.083 \text{ frequency of gene for blue}$$

$(0.083)^2 = 0.007$, or 0.7% babies with blue eyes.

5. Because 30% would be nontasters (the recessive trait), the frequency of the gene for nontasting would be the square root of this figure, or 54.8%. This would leave 45.2% as the frequency of the dominant gene for tasting. Homozygous tasters would be the square root of this, or 20.4%. Heterozygous tasters would be the balance, or 49.6%.

$$1.00 - (0.30 + 0.204) = 0.496$$

6. If 4% are albinos the frequency in the population would be the square root of 0.04, or 0.20. With half fertility the coefficient k would equal 0.5. Hence, after eight generations the percentage of albino minks would be:

$$q_8 = \frac{0.20}{1 + 0.5 \times 8 \times 0.20} = 0.111 \text{ gene frequency}$$

$$(0.111)^2 = 0.012 \text{ or } 1.2\% \text{ albinos}$$

7. Since $\frac{1}{400}$ is 0.25% we can calculate as follows:

$$q_s = \frac{0.0025}{1 + 6 \times 0.0025} = 0.002 \text{ gene frequency which is } \frac{1}{500}$$

Carriers would be $\frac{1}{500} \times 2 = \frac{1}{250}$, or $0.002 \times 2 = 0.004$

8. New Zealand, because a smaller number of rabbits was introduced there. The likelihood of variation from the original group is greater when those introduced were small in quantity.

9. Migration, invasion, differential reproduction, sexual selection, natural selection, and differential mutation all could have played a part.

CHAPTER 18

1. Many different traits could be selected. Body stature, body weight, intelligence, disease susceptibility, and so on. Such factors as diet, disease, training, and other environmental factors would be involved.

2. The trait must have reduced penetrance so that the daughter got the gene from her father, but did not show it, yet it was expressed in her children.

3. About 5%. About 25% would be homozygous and 20% of these would express the trait.

4. Breed them to other rumpless chickens from a breed in which this trait is inherited. If offspring are all normal, the chicken is a phenocopy; if offspring are rumpless, the condition must be due to the gene.

5. Heredity must be involved because of the great difference between the identicals and fraternals, yet because the identicals are not 100% in concordance, some environmental factors must be necessary for the expression of the genes.

6. Sex plays an important role in the expression of many traits. Moreover, because all identicals are of the same sex, the fraternals of opposite sex cannot be considered for a valid comparison.

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